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NEWS 4	JUN 26	NUTRACEUT and PHARMAML no longer updated
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NEWS 6	JUN 29	EPFULL adds Simultaneous Left and Right Truncation (SLART) to AB, MCLM, and TI fields
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=> s cyp (3a) engineered cell
L1            3 CYP (3A) ENGINEERED CELL
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=> dup rem l1
PROCESSING COMPLETED FOR L1
L2            1 DUP REM L1 (2 DUPLICATES REMOVED)

=> d bib abs

L2   ANSWER 1 OF 1  BIOSIS  COPYRIGHT (c) 2009 The Thomson
Corporation  on STN
     DUPLICATE 1
AN   2001:501821  BIOSIS
DN   PREV200100501821
TI   The use of genetically engineered cells for assessing
CYP2D6-related
     polymorphic effects.
AU   Coecke, S. [Reprint author]; Bogni, A.; Langezaal, I.; Worth,
A.; Hartung,
     T.; Monshouwer, M.
CS   ECV AM, Institute for Health and Consumer Protection, European
Commission
     Joint Research Centre, 21020, Ispra, VA, Italy
     sandra.coecke@jrc.it
SO   Toxicology In Vitro, (August-October, 2001) Vol. 15, No. 4-5,
pp. 553-556.
     print.
     CODEN: TIVIEQ. ISSN: 0887-2333.
DT   Article
LA   English
ED   Entered STN: 24 Oct 2001
     Last Updated on STN: 23 Feb 2002
AB   As an example of advanced testing in the field of metabolism in
an
     industrial environment, the introduction of some novel
approaches,
     including the use of genetically engineered cell lines
     for assessing CYP 2D6-related polymorphic effects is
     illustrated.  In this paper, it is demonstrated that novel in
vitro test
     systems can be developed by using these genetically engineered
cell lines
     for evaluating the potential risks associated with proprietary
drugs
     (especially if their metabolism depends to a high extent on CYP
2D6).
     Moreover, it is demonstrated that, by the use of these in vitro
methods,
     issues such as polymorphism, for which no animal models are
available, can
     be assessed in such a way that predictions can be made on
adverse effects
     which, up to now, could only be detected during clinical trials.
 Through
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the use of these new biotechnological in vitro metabolism models, clinically relevant data can be obtained for a scientifically-based human risk assessment, and animal use can be reduced.

=> FIL STNGUIDE
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 12.53 | 12.75

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FULL ESTIMATED COST | 0.28 | 13.03

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L1 3 S CYP (3A) ENGINEERED CELL
L2 1 DUP REM L1 (2 DUPLICATES REMOVED)

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=> s hepatocyte and recombin?
L3 5627 HEPATOCYTE AND RECOMBIN?

=> s l3 and CYP
L4 81 L3 AND CYP

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=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           51 DUP REM L4 (30 DUPLICATES REMOVED)

=> s l5 and pY<=2004
L6           28 L5 AND PY<=2004

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 28 ANSWERS - CONTINUE? Y/(N):y

L6   ANSWER 1 OF 28  BIOSIS  COPYRIGHT (c) 2009 The Thomson
Corporation  on STN
AN   2006:77789  BIOSIS
DN   PREV200600084530
TI   Cytochrome 209: A new hepatic target of immune reactions after
orthotopic
     liver transplantation.
AU   Grazia Clemente, Maria; Vajro, Pietro; Musu, Maria P.; Mandato,
Claudia;
     di Cosmo, Nicolina; Porqueddu, Patrizia; Cicotto, Lucia; Zancan,
Lucia;
     Gridelli, Bruno; De Virgiliis, Stefano
SO   Gastroenterology, (APR 2004) Vol. 126, No. 4, Suppl. 2, pp.
     A304.
     Meeting Info.: Digestive Disease Week/105th Annual Meeting of the
     American-Gastroenterological-Association. New Orleans, LA, USA.
May 16
     -20, 2004. Amer Gastroenterol Assoc.
     CODEN: GASTAB. ISSN: 0016-5085.
DT   Conference; (Meeting)
     Conference; Abstract; (Meeting Abstract)
LA   English
ED   Entered STN: 25 Jan 2006
     Last Updated on STN: 25 Jan 2006
AB   Background.  Typical and atypical serum autoantibodies have been
recently
     reported as important diagnostic tools in all cases of "de novo"
     autoimmune hepatitis (AH), a new type of late graft dysfunction
observed
     after orthotopic liver transplantation (OLT) for non autoimmune
liver
     diseases (NALD).  Whether "de novo" AH after OLT is a true
autoimmune
     disorder or represents an immune reaction against "non-self'
antigens is
     still a moot point Aim: to investigate the appearance of serum
     autoantibodies during the follow-up in 46 Italian patients who
underwent
     OLT for NALD.  Methods.  Indirect immunofluorescence (IF) on
different
     tissue sections and Western blotting (WB) of human liver
subcellular
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protein fractions and recombinant antigen preparations. Results. Ten of 46 (21%) patients developed serum autoantibodies after OLT. In IF experiments, anti-nuclear antibodies (ANA) were detected in 5 (titer range 1:40 - >1:1000), anti-smooth muscle antibodies in 4 patients (titer range 1:320 - >1:1000). One patient was positive for anti-liver microsomal (LM; titer >1:1000) antibodies characterized by a new fluorescent pattern involving the cytoplasm of hepatocytes of the centrilobular area but sparing renal tubular cells. In WB experiments using liver microsomal subcellular preparations this new LM antibody specifically reacted with a protein band at approximately 52 kd molecular weight which was identified as cytochrome P450 2C19 (CYP 2C19) by using recombinant protein preparations. Only 3 (6,5%) of our patients had clinical, histological and therapeutic criteria of "de novo" AH after OLT, At the time of graft dysfunction they showed 3 different autoantibody profiles: one with typical ANA + SMA, one with atypical LKC and one with new LM anti CYP 209 Conclusions, Typical, atypical and new autoantibodies were detected during the follow-up in several of our OLT patients. Only in one third, however, the presence of autoantibodies was associated to other diagnostic features of "de novo" AH. The discovery of CYP 2C19 as a new hepatic target involved in human autoimmune pathology 411 help to clarify the pathogenic mechanisms underlying 'de novo" AH after OLT.

L6 ANSWER 2 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2004:356344 BIOSIS
DN PREV200400361311
TI Can hepatoma cell lines be redifferentiated to be used in drug metabolism studies?.
AU Martinez-Jimenez, Celia P.; Jover, Ramiro; Gomez-Lechon, Maria Jose; Castell, Jose V. [Reprint Author]
CS Hosp La FeCtr InvestUnidad Hepatol Expt, Univ Valencia, Avda Campanar 21, Valencia, 46009, Spain
jose.castell@uv.es
SO ATLA Alternatives to Laboratory Animals, (June 2004) Vol. 32, No. Suppl. 1A, pp. 65-74. print.
ISSN: 0261-1929 (ISSN print).

DT Article
LA English
ED Entered STN: 5 Sep 2004
Last Updated on STN: 5 Sep 2004
AB Knowledge of metabolism, enzymes so far involved, and potential enzyme-inhibiting or enzyme-inducing properties of new compounds is a key issue in drug development. Primary cultured hepatocytes, cytochrome P450 (CYP)-engineered cells and hepatoma cell lines are currently being used for this purpose, but only primary cultures can produce a metabolic profile of a drug similar to that found in vivo and can respond to inducers. Because of their limited accessibility, alternatives to replace human hepatocytes are currently being explored, including the immortalisation of hepatocytes by using different strategies (i.e. SV40 T-large antigen, conditionally immortalised hepatocytes, transfection with c-myc, cH-ras, N-ras oncogenes, transgenic animals over-expressing growth factors or oncogenes and cre-lox recombination/excision). However, none of the resulting cells has the desirable phenotypic characteristics to replace primary cultures in drug metabolisms studies. We investigated why these differentiated human hepatomas do not express CYP genes and found that the levels of certain key transcription factors clearly differ from those found in hepatocytes. It was then conceivable that re-expression of one (or more) of these transcription factors could lead to an efficient transcription of CYP genes. The feasibility of this hypothesis was demonstrated by genetic engineering of Hep G2 cells with liver-enriched transcription factors followed by the analysis of the expression of the most relevant human CYPs.

L6 ANSWER 3 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2004:282028 BIOSIS
DN PREV200400282239
TI Inhibition of carcinogen-bioactivating cytochrome P450 1 isoforms by amiloride derivatives.
AU Sparfel, Lydie [Reprint Author]; Huc, Laurence; Le Vee, Marc; Desille, Mireille; Lagadic-Gossmann, Dominique; Fardel, Olivier

CS INSERMU456Fac Sci Pharmaceut & Biol, Univ Rennes 1, 2 Ave Prof Leon
Bernard, F-35043, Rennes, France
lydie.sparfel@rennes.inserm.fr
SO Biochemical Pharmacology, (May 1 2004) Vol. 67, No. 9, pp. 1711-1719. print.
CODEN: BCPCA6. ISSN: 0006-2952.
DT Article
LA English
ED Entered STN: 9 Jun 2004
Last Updated on STN: 9 Jun 2004
AB We examined the effects of amiloride derivatives, especially 5-(N-ethyl-N-isopropyl)amiloride (EIPA), on the activity of cytochrome P450 (CYP) 1 isoforms, known to metabolize carcinogenic polycyclic aromatic hydrocarbons (PAHs), such as benzo(a)pyrene (BP), into mutagenic metabolites and whose cellular expression can be induced through interaction of PAHs with the arylhydrocarbon receptor. EIPA was found to cause a potent and dose-dependent inhibition of CYP1-related ethoxyresorufine O-deethylase (EROD) activity in both liver cells and microsomes. It also markedly reduced activity of human recombinant CYP1A1 enzyme through a competitive mechanism; activities of other human CYP1 isoforms, i.e. CYP1A2 and CYP1B1, were also decreased. However, EIPA did not affect BP-mediated induction of CYP1A1 mRNA and protein levels in rat liver cells, likely indicating that EIPA does not block activation of the arylhydrocarbon receptor by PAHs. Inhibition of CYP1 activity by EIPA was associated with a decreased metabolism of BP, a reduced formation of BP-derived DNA adducts and a diminished BP-induced apoptosis in liver cells. The present data suggest that amiloride derivatives, such as EIPA, may be useful for preventing toxicity of chemical carcinogens, such as PAHs, through inhibition of CYP1 enzyme activity.

L6 ANSWER 4 OF 28 BIOSIS
AN 2004:103417 BIOSIS
DN PREV200400103477
TI Rapid determination of enzyme activities of recombinant human

cytochromes P450, human liver microsomes and hepatocytes.
AU Ghosal, Anima [Reprint Author]; Hapangama, Neil; Yuan, Yuan; Lu, Xiaowen;
Horne, Debra; Patrick, James E.; Zbaida, Shmuel
CS Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute,
2015 Galloping Hill Road, 1945, Mail Stop: K-15-1, Kenilworth, NJ, 07033,
USA
anima.ghosal@spcorp.com
SO Biopharmaceutics & Drug Disposition, (December 2003) Vol. 24, No. 9, pp. 375-384. print.
ISSN: 0142-2782 (ISSN print).
DT Article
LA English
ED Entered STN: 18 Feb 2004
Last Updated on STN: 18 Feb 2004
AB Cytochrome P450 (CYP) substrates that yield fluorescent metabolites were used for rapid screening of drug metabolism activities of 13 recombinant human cytochromes P450, human liver microsomes and human hepatocytes. Reproducible results were obtained using a fluorescent plate reader (CytoFluor) more expediently than those generated using conventional HPLC methods. Typically, results for 96 samples were obtained with the plate reader in less than 10 min as opposed to 15-35 min/sample required by conventional HPLC. The fluorescent substrates used to measure CYP activities were as follows: 3-cyano-7-ethoxycoumarin (CEC) for CYP1A1, CYP1A2, CYP2C9 and CYP2C19; 7-ethoxyresorufin (7-ER) for CYP1A1, CYP1A2 and CYP1B1; 3-(2-(N,N-diethyl-N-methylammonium)ethyl)-7-methoxy-4-methylcoumarin (AMMC) for CYP2D6; dibenzylfluorescein (DBF) for CYP3A4, CYP3A5 and CYP2C8; 7-methoxy-4-trifluoromethylcoumarin (7-MFC) for CYP2E1, CYP2B6 and CYP2C18; and coumarin for CYP2A6. The chemical inhibition and correlation data indicated that the following substrates can be used as specific functional probes for individual cytochrome P450 present in human liver microsomes: coumarin for CYP2A6 (r=0.82), AMMC for CYP2D6 (r=0.83) and DBF for CYP3A4 (r=0.92). The fluorescent plate reader was found to be useful for the rapid assessment of CYP activities (positive control) in

both intact cells and subcellular fractions.

L6 ANSWER 5 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2002:90733 BIOSIS
DN PREV200200090733
TI Predicting drug pharmacokinetics in humans from in vitro metabolism
studies.
AU McGinnity, D. F. [Reprint author]; Riley, R. J.
CS Physical and Metabolic Science, AstraZeneca R and D Charnwood, Loughborough, LE11 5RH, UK
dermot.mcginnity@astrazeneca.com
SO Biochemical Society Transactions, (May, 2001) Vol. 29, No. 2, pp. 135-139. print.
CODEN: BCSTB5. ISSN: 0300-5127.
DT Article
LA English
ED Entered STN: 24 Jan 2002
Last Updated on STN: 25 Feb 2002
AB The pharmaceutical industry is committed to market safer drugs with fewer
side effects, predictable pharmacokinetic properties and quantifiable
drug-drug interactions. There is an increasing need to develop robust,
enhanced-throughput in vitro assays, which accurately extrapolate to
humans. The major drug metabolizing human hepatic cytochrome P450s (CYPs;
CYP1A2, 2C9, 2C19, 2D6 and 3A4) have been co-expressed functionally in
Escherichia coli with human NADPH-cytochrome P450 reductase and validated
as surrogates to their counterparts in human liver microsomes (HLM) with
respect to their kinetic and inhibition properties. Using these
recombinant enzymes, fully automated in vitro assays to assess
CYP inhibition and determine the enzymology of drug oxidation have
been developed and validated. IC50 values determined for a series of test
compounds in HLM and recombinant CYPs were similar (r2=0.9,
P<0.001). There was a good correlation between the sum of individual
CYP intrinsic clearance (Clint) and HLM Clint (r2=0.8, P<0.001)
for ten prototypic substrates for which clearance was CYP
-dependent. Several in vitro incubation milieu (e.g. CYPs, HLM, human
hepatocytes) are routinely used and the level of non-specific binding was
investigated with respect to effects on Km and Ki determinations. There

were clear correlations between binding and lipophilicity (logD7.4) for a selection of bases (r2=0.98, P<0.001) and acids (r2=0.79, P<0.001) that may allow prediction of this property. Our laboratory has shown that recombinant enzymes are suitable for 'frontline' predictive human metabolism studies in early drug discovery.

L6 ANSWER 6 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2001:552056 BIOSIS
DN PREV200100552056
TI Effects of heavy metals and 3-methylcholanthrene on expression and induction of CYP1A1 and metallothionein levels in trout (Oncorhynchus mykiss) hepatocyte cultures.
AU Risso-de Faverney, Christine; Lafaurie, Marc; Girard, Jean-Pierre; Rahmani, Roger [Reprint author]
CS Laboratoire de Pharmaco-Toxicologie Cellulaire et Moleculaire, Centre de Recherche INRA, 41, Bd du Cap, 06606, Antibes Cedex, France rahmani@antibes.inra.fr
SO Environmental Toxicology and Chemistry, (September, 2000) Vol. 19, No. 9, pp. 2239-2248. print. CODEN: ETOCDK. ISSN: 0730-7268.
DT Article
LA English
ED Entered STN: 21 Nov 2001 Last Updated on STN: 25 Feb 2002
AB Induction of both CYP1A1 and metallothioneins (MTs) in fish liver is increasingly being used in ecotoxicological studies. The interaction of heavy metals (Cd, Cu, Zn, Pb) with the CYP1A induction response and MT levels was studied in trout (Oncorhynchus mykiss) hepatocyte cultures. Cells were exposed to 3-methylcholanthrene (3-MC) or to increasing heavy metal concentrations or to a mixture of both (3-MC and one heavy metal). Metal cytotoxicity was assessed by the neutral red test. Ranking of toxicity was Cd(II)>Cu(II)>Zn(II)>Pb(II) (EC50: 45, 222, 873, and 945 muM, respectively). CYP1A1 expression was monitored by ethoxyresorufin-O-deethylase (EROD) activity as well as by Western and Northern blots. As expected, 3-MC induced EROD activity in a time- and

dose-dependent manner (maximal induction 5 times that of the control at 0.5 muM and after a 72-h exposure period). These data were confirmed by Western blot (intense band of 55-60 KDa) and Northern blot analyses. Induction caused by 0.5 muM 3-MC was reduced to less than 50% of control by the concomitant exposure to Cd, Cu, Pb, or Zn (EC50: from 1 muM for Cd(II) to 18 muM for Pb(II)). The MTs were significantly induced in hepatocytes exposed to heavy metals for 24 h. In the presence of 3-MC (0.5 muM), MT levels were significantly lower than those found in cells treated with metals alone at 24 h only. Our results lead to the conclusion that heavy metals significantly affect CYP expression and that a CYP1A1 inducer (3-MC) can modulate the induction of MTs. These data have to be taken into consideration in biomarker monitoring.

L6 ANSWER 7 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2001:433893 BIOSIS
DN PREV200100433893
TI Establishment of a human hepatocyte line (OUMS-29) having CYP 1A1 and 1A2 activities from fetal liver tissue by transfection of SV40 LT.
AU Fukaya, Ken-Ichi; Asahi, Satoru; Nagamori, Seishi; Sakaguchi, Masakiyo; Gao, Chong; Miyazaki, Masahiro; Namba, Masayoshi [Reprint author]
CS Department of Cell Biology, Institute of Cellular and Molecular Biology, Okayama University Medical School, Okayama, 700-8558, Japan mnamba@med.okayama-u.ac.jp
SO In Vitro Cellular and Developmental Biology Animal, (May, 2001) Vol. 37, No. 5, pp. 266-269. print. ISSN: 1071-2690.
DT Article
LA English
ED Entered STN: 12 Sep 2001 Last Updated on STN: 22 Feb 2002
AB Immortalized human hepatocytes that can retain functions of drug-metabolizing enzymes would be useful for medical and pharmacological studies and for constructing an artificial liver. The aim of this study was to establish immortalized human hepatocyte lines having differentiated liver-specific functions. pSVneo deoxyribonucleic acid,

which contains large and small T genes in the early region of simian virus 40, was introduced into hepatocytes that had been obtained from the liver of a 21-wk-old fetus. Neomycin-resistant immortalized colonies were cloned and expanded to mass cultures to examine hepatic functions. Cells were cultured in a chemically defined serum-free medium, ASF104, which contains no peptides other than recombinant human transferrin and insulin. As a result, an immortal human hepatocyte cell line (OUMS-29) having liver-specific functions was established from one of the 13 clones. Expression of CYP 1A1 and 1A2 messenger ribonucleic acid by the cells was induced by treatment with benz(a)pyrene, 3-methylcholanthrene, and benz(a)anthracene. OUMS-29 cells had both the polycyclic aromatic hydrocarbon receptor (AhR) and AhR nuclear translocator. Consequently, 7-ethoxyresorufin deethylase activity of the cells was induced time- and dose-dependently by these polycyclic aromatic hydrocarbons. This cell line is expected to be instrumental as an alternative method in animal experiments for studying hepatocarcinogenesis, drug metabolisms of liver cells, and hepatic toxicology.

L6 ANSWER 8 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2001:342706 BIOSIS
DN PREV200100342706
TI Indirect cytotoxicity of flucloxacillin toward human biliary epithelium via metabolite formation in hepatocytes.
AU Lakehal, Fatima; Dansette, Patrick M.; Becquemont, Laurent; Lasnier, Elisabeth; Delelo, Roland; Balladur, Pierre; Poupon, Raoul; Beaune, Philippe H.; Housset, Chantal [Reprint author]
CS Faculte de Medecine Saint-Antoine, Unite INSERM U402, Paris, France
chantal.housset@st-antoine.inserm.fr
SO Chemical Research in Toxicology, (June, 2001) Vol. 14, No. 6, pp. 694-701. print.
CODEN: CRTOEC. ISSN: 0893-228X.
DT Article
LA English
ED Entered STN: 18 Jul 2001

Last Updated on STN: 19 Feb 2002

AB Flucloxacillin, an isoxazolyl-penicillin, causes cholestasis and biliary epithelium injury. The aim of the study was to determine whether flucloxacillin, either directly or through metabolite formation, may induce cytotoxicity in hepatic or biliary cells. Cytotoxicity was assessed by lactate dehydrogenase release in primary cultures of human hepatocytes and of gallbladder-derived biliary epithelial cells (BEC).

Metabolite production in microsome and cell preparations was analyzed by chromatography, nuclear magnetic resonance spectroscopy, and mass spectrometry. While flucloxacillin induced no direct cytotoxicity in any of the hepatocyte (n=12) and BEC (n=19) preparations, the conditioned media from cultured hepatocytes preincubated with flucloxacillin (50-500 mg/L) triggered a significant increase in lactate dehydrogenase release over controls in apprx50% of BEC preparations (7/12), and this effect depended upon flucloxacillin concentration.

Remaining BEC preparations exhibited no toxic response. Cytotoxicity in BEC preparations (9/13) was also induced by the supernatants of human liver microsomes and of recombinant human cytochrome P450 (CYP)3A4 preincubated with flucloxacillin (500 mg/L). Supernatants from both liver microsome and CYP3A4 preparations contained one major metabolite which was identified as 5'-hydroxymethylflucloxacillin. The production of this metabolite was inhibited following CYP3A4 inhibition by troleandomycin in human liver microsomes, and markedly enhanced following CYP3A induction by dexamethasone in rat liver microsomes. As opposed to BEC, cultured hepatocytes displayed significant CYP3A activity and produced low amounts of this metabolite. The purified metabolite (0.01-5 mg/L) exerted toxic effects in BEC but not in hepatocytes. In conclusion, hepatocytes mainly via CYP3A4 activity, generate flucloxacillin metabolite(s) including 5'-hydroxymethylflucloxacillin that may induce cytotoxicity in susceptible BEC. These metabolic events may contribute to

the pathogenesis of drug-induced cholangiopathies.

L6 ANSWER 9 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2001:320260 BIOSIS
DN PREV200100320260
TI In vitro stimulation of warfarin metabolism by quinidine: Increases in the
formation of 4'- and 10-hydroxywarfarin.
AU Ngui, Jason S.; Chen, Qing; Shou, Magang; Wang, Regina W.; Stearns, Ralph
A.; Baillie, Thomas A.; Tang, Wei [Reprint author]
CS Department of Drug Metabolism, Merck and Co., RY800-B211, Rahway, NJ,
07065, USA
wei_tang@merck.com
SO Drug Metabolism and Disposition, (June, 2001) Vol. 29, No. 6,
pp. 877-886. print.
CODEN: DMDSAI. ISSN: 0090-9556.
DT Article
LA English
ED Entered STN: 4 Jul 2001
Last Updated on STN: 19 Feb 2002
AB It has been demonstrated that the activity of cytochrome P450 (CYP
)3A4 in certain cases is stimulated by quinidine (positive heterotropic
cooperativity). We report herein that the 4'- and 10-hydroxylation of S-
and R-warfarin are enhanced in human liver microsomal incubations
containing quinidine. These reactions were catalyzed by CYP3A4, based on
data derived from immunoinhibitory studies, with 4'-hydroxylation being
preferentially associated with S-warfarin and 10-hydroxylation with
R-warfarin. The 4'-hydroxylation of S-warfarin and 10-hydroxylation of
R-warfarin increased with increasing quinidine concentrations and
maximized at apprx3- and 5-fold the values of controls, respectively.
Stimulatory effects of quinidine also were observed with
recombinant CYP3A4, suggesting that increases in warfarin
metabolism were due to quinidine-mediated enhancement of CYP3A4 activity.
This positive cooperativity of CYP3A4 was characterized by a 2.5-fold
increase in Vmax for the 4'-hydroxylation of S-warfarin and a 5-fold
increase in Vmax for the 10-hydroxylation of R-warfarin, with little
change in Km values. Conversely, Vmax for the 3-hydroxylation of

quinidine was not influenced by the presence of warfarin. These results are consistent with previous findings suggesting the existence of more than one binding site in CYP3A4 through which interactions may occur between substrate and effector at the active site of the enzyme. Such interactions were subsequently illustrated by a kinetic model containing two binding domains, and a good regression fit was obtained for the experimental data. Finally, stimulation of warfarin metabolism by quinidine was investigated in suspensions of human hepatocytes, and increases in the formation of 4'- and 10-hydroxywarfarin again were observed in the presence of quinidine, indicating that this type of drug-drug interaction occurs in intact cells.

L6 ANSWER 10 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2001:151846 BIOSIS
DN PREV200100151846
TI Cytochrome P450 regulation by hepatocyte nuclear factor 4 in human hepatocytes: A study using adenovirus-mediated antisense targeting.
AU Jover, Ramiro; Bort, Roque; Gomez-Lechon, Maria J.; Castell, Jose V.
[Reprint author]
CS Unidad de Hepatologia Experimental, Centro de Investigacion, Hospital Universitario La Fe, SVS, Avda. Campanar 21, E-46009, Valencia, Spain
Jose.Castell@uv.es
SO Hepatology, (March, 2001) Vol. 33, No. 3, pp. 668-675. print.
CODEN: HPTLD9. ISSN: 0270-9139.
DT Article
LA English
ED Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002
AB Hepatocyte nuclear factor 4 (HNF4) is a member of the nuclear receptor super-family that has shown activating effects on particular cytochrome P450 (CYP) promoters from several species. However, its role in the regulation of human CYPs in the liver is still poorly understood, as no comprehensive studies in human-relevant models have been

performed. In the present study, we have investigated whether HNF4 plays a general role in the expression of 7 major CYP genes in primary cultured human hepatocytes. To this end, we developed an adenoviral vector for efficient expression of HNF4 antisense RNA. Transduction of human hepatocytes with the recombinant adenovirus resulted in a time-dependent increase in the antisense transcript, followed by a concomitant decrease in apolipoprotein C III mRNA (a target gene of HNF4). Specificity was confirmed by showing that increasing levels of HNF4 antisense RNA resulted in the reduction of HNF4 protein, whereas retinoic X receptor-alpha (RXRalpha), the closest homologous member of the nuclear receptor super-family, was unaffected. Analysis of CYP gene expression in human hepatocytes transfected with HNF4 antisense RNA revealed singular behaviors: (1) CYP3A4, CYP3A5, and CYP2A6 showed an important, dose-dependent down-regulation on blockage of HNF4 translation; (2) a moderate inhibition of CYP2B6, CYP2C9, and CYP2D6 expression was observed (40%-45% reduction); (3) the levels of CYP2E1 were not affected even in the absence of this transcription factor. In conclusion, using an original strategy (efficient antisense RNA expression vector), our study shows that HNF4 is a general regulator supporting the expression of major drug-metabolizing CYPs in human hepatocytes.

L6 ANSWER 11 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

AN 2001:70817 BIOSIS

DN PREV200100070817

TI Regulation of CYP2B1 expression by endogenous nitric oxide.

AU Morgan, Edward T. [Reprint author]; Peng, Ning [Reprint author]; Ferrari, Luc

CS Dept Pharmacology, Emory University, Atlanta, GA, 30047, USA

SO British Journal of Pharmacology, (October, 2000) Vol. 131, No. Proceedings Supplement, pp. 17P. print.
Meeting Info.: Meeting of the British Pharmacological Society. Cardiff, Wales, UK. July 12-14, 2000. British Pharmacological Society.

CODEN: BJPCBM. ISSN: 0007-1188.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 7 Feb 2001
Last Updated on STN: 12 Feb 2002

L6 ANSWER 12 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN
AN 2000:426665 BIOSIS
DN PREV200000426665
TI Drug metabolism capacity of the novel B16A2 human hepatoma cell line.
AU Guyomard, Claire [Reprint author]; Langouet, Sophie; Corcos, Laurent;
Galisteo, Mila; Gay-Feutry, Croisine [Reprint author]; Chesne, Christophe
[Reprint author]; Guillouzo, Andre
CS BIOPREDIC International, 14-18 Rue Jean Pecker, 35000, Rennes, France
SO Drug Metabolism Reviews, (2000) Vol. 32, No. Supplement 1, pp. 59. print.
Meeting Info.: Drug Metabolism Workshop of the International Society for
the Study of Xenobiotics. St. Andrews, Scotland. June 11-16, 2000.
International Society for the Study of Xenobiotics.
CODEN: DMTRAR. ISSN: 0360-2532.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 Oct 2000
Last Updated on STN: 10 Jan 2002

L6 ANSWER 13 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN
AN 1998:441393 BIOSIS
DN PREV199800441393
TI Detoxication of aflatoxin B1 as a model for carcinogen metabolism.
AU Langouet, Sophie [Reprint author]; Johnson, William W.; Guillouzo, Andre;
Guengerich, F. Peter
CS INSERM U456, Universite de Rennes I, Faculte des Sciences Pharmaceutiques
et Biologiques, 2 Avenue du Professeur Leon Bernard, 35043 Rennes Cedex,
France
SO In Vitro and Molecular Toxicology, (Spring, 1998) Vol. 11, No. 1, pp. 95-101. print.

ISSN: 1097-9336.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 7 Oct 1998
Last Updated on STN: 5 Nov 1998
AB Aflatoxin B1 (AFB1) is a powerful carcinogen that plays an important role in the etiology of human liver cancers. This procarcinogen is activated by cytochrome P450 (CYP) enzymes to produce a number of products, including the exo-8,9-epoxide that is responsible for its mutagenic and hepatocarcinogenic potential. Primarily human CYP3A4 and, to a lesser extent, CYP1A2 are involved in activation of AFB1 to the epoxide and formation to less dangerous metabolites. Analysis of metabolites formed by primary human hepatocyte cultures clearly shows that only cells from glutathione (GSH) transferase M1-1-positive individuals are able to conjugate the epoxide with GSH. This observation is in agreement with the variation of enzyme efficiency of individual recombinant GSH transferases, which is in the order (rat) 10-10 mchgt 3-3 > (human) M1-1 > T1-1 > A1-1 > P1-1 > A2-2. Hydrolysis of the epoxide constitutes another detoxication pathway against AFB1 and is mainly due to spontaneous reaction rather than epoxide hydrolase catalysis, since rat and human epoxide hydrolases Show very little rate acceleration of hydrolysis of AFB1 epoxide. The effects of two potent chemoprotective agents, oltipraz (a synthetic dithiolethione) and sulforaphane (an isothiocyanate), were also investigated using primary cultures of human hepatocytes. The data suggest that the protection exerted by these two compounds is probably due to inhibition of activation of AFB1, in addition to GSH transferase-dePendent inactivation of the carcinogenic exo-epoxide. Indeed, both CYP1A and 3A4 are inhibited by oltipraz and sulforaphane, while GSH transferases A1 and A2 are primarily induced, compared to GSH transferase M1.

L6 ANSWER 14 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on

STN
AN 1998:140460 BIOSIS
DN PREV199800140460
TI Human hepatocyte growth factor down-regulates the expression of cytochrome P450 isozymes in human hepatocytes in primary culture.
AU Donato, M. Teresa; Gomez-Lechon, M. Jose [Reprint author]; Jover, Ramiro; Nakamura, Toshikazu; Castell, Jose V.
CS Unidad de Hepatol. Experimental, Centro de Investigacion, Hospital Universitario La Fe, Avda. Campanar 21, 46009 Valencia, Spain
SO Journal of Pharmacology and Experimental Therapeutics, (Feb., 1998) Vol. 284, No. 2, pp. 760-767. print.
CODEN: JPETAB. ISSN: 0022-3565.
DT Article
LA English
ED Entered STN: 20 Mar 1998
Last Updated on STN: 20 Mar 1998
AB This study examines the effects of recombinant human hepatocyte growth factor (HGF), a potent mitogen for hepatocytes, on the cytochrome P450 (CYP) system and conjugating reactions in cultured human hepatocytes. The time course of HGF effects on CYP1A1/2 (7-ethoxyresorufin O-deethylase) activity revealed that maximal inhibition was observed at 96 hr of culture. HGF produced a general decrease in the activity of all the CYP isozymes studied, namely CYP1A1/2 (7-ethoxyresorufin O-deethylase), CYP2B6 (7-benzoxyresorufin O-debenzylase), CYP2A6 (coumarin 7-hydroxylase), CYP2E1 (p-nitrophenol hydroxylase) and CYP3A4 (testosterone 6beta-hydroxylase). In contrast, UDP-glucuronyltransferase and glutathione S-transferase activities and reduced glutathione levels were not modified significantly by the factor. When hepatocytes were treated with inducers, marked increases in the specific activities of CYP1A1/2 by 3-methylcholanthrene and CYP3A4 by rifampicin were observed, and these inductive effects were greatly reduced in the presence of HGF. Furthermore, CYP1A2 and CYP3A4 protein levels also dropped in the presence of HGF both in control and induced hepatocytes. The observed changes in the activity and protein levels of CYP1A2 and CYP3A4 correlated with a reduction in the specific messenger

RNA levels both in control, 3-methylcholanthrene-treated (for CYP1A2) and
rifampicin-treated (for CYP3A4) hepatocytes, which thus suggested that HGF
could down-regulate CYP expression at a pretranslational level.

L6 ANSWER 15 OF 28 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN
AN 1996:434957 BIOSIS
DN PREV199699148563
TI Interferon gamma down-regulates cytochrome P450 3A genes in primary
cultures of well-differentiated rat hepatocytes.
AU Tapner, Michael; Liddle, Chris; Goodwin, Bryan; George, Jacob; Farrell,
Geoffrey C.
CS Storr Liver Unit, Dep. Med., Westmead Hosp., Westmead, NSW 2145, Australia
SO Hepatology, (1996) Vol. 24, No. 2, pp. 367-373.
CODEN: HPTLD9. ISSN: 0270-9139.
DT Article
LA English
ED Entered STN: 26 Sep 1996
Last Updated on STN: 5 Nov 1996
AB Administration of interferons of both the gamma and alfa/beta classes
down-regulates hepatic cytochrome P450 (CYP) genes when
administered to humans or rats. in male rats, interferons decrease
expression of CYP3A2 at a pretranslational level, but because interferons
also release other cytokines in vivo, it is unclear whether this is a
direct effect on hepatocytes. We therefore examined the effects of rat
recombinant interferon gamma (IFN-gamma) on CYP3A2, other 3A
genes, and 2C11 in stable primary cultures of male rat hepatocytes.
Hepatocytes were cultured on matrigel in Williams' E, and messenger RNAs
(mRNAs) for 3A2, 3A1-like CYPs, and 2C11 mRNA were determined by RNase
protection assays. CYP3A and 2C11 proteins were immunoquantified, and
their catalytic activities were estimated by testosterone hydroxylation
pathways. In control cells, 3A2 mRNA decreased initially but then
recovered, and stable levels (15% of freshly isolated cells) were attained
between days 3 and 7. Phenobarbital increased 3A2 mRNA to 60-120% values

of freshly isolated cells, and mRNA for 3A1-like CYPs were increased 20-fold. In both control and phenobarbital-treated hepatocytes, rat recombinant IFN-gamma (33 U/mL) reduced mRNA for 3A2 and 3A1-like CYPs, as well as 3A protein and testosterone 6-beta-hydroxylase activity. Interferon had no effect on CYP2C11 at mRNA or protein levels in untreated cells, although a reduction in 2C11 protein was evident in phenobarbital-treated cultures. It is concluded that interferon directly alters expression of constitutive and inducible CYP3A genes in well-differentiated male rat hepatocytes in culture, but has no effect on constitutive expression of CYP2C11.

L6 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2005:291473 CAPLUS
DN 143:132376
TI Discovery, characterization, and significance of the cytochrome P450 ω-hydroxylase pathway of vitamin E catabolism
AU Parker, Robert S.; Sontag, Timothy J.; Swanson, Joy E.; McCormick, Charles C.
CS Division of Nutritional Sciences, Cornell University, Ithaca, NY, 14853, USA
SO Annals of the New York Academy of Sciences (2004), 1031(Vitamin E and Health), 13-21
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal; General Review
LA English
AB A review. Tocopherols are known to undergo metabolism to phytyl chain-shortened metabolites excreted in urine. We sought to characterize the pathway, including associated enzymes, involved in this biotransformation. We previously found that human hepatoblastoma (HepG2) cultures metabolized tocopherols to their corresponding short-chain carboxychromanols. Putative metabolites of γ-tocopherol that contained intact chromanol moieties were structurally identified using HepG2 cultures and electron impact gas chromatog.-mass spectrometry. A microsomal assay for synthesis of the initial ω-oxidation metabolites was developed and used to screen several recombinant human liver cytochrome P 450 isoenzymes for ω-hydroxylase activity. Seven

metabolites of γ-tocopherol were identified in HepG2 cultures, including 13'-hydroxy-γ-TOH and all six carboxychromanols predicted by sequential ω-oxidation truncation. Rat and human liver microsomes catalyzed synthesis of 13'-OH- and 13'-COOH-γ-TOH, but not other metabolites, in the presence of NADPH. Inclusion of NAD favored synthesis of the 13'-COOH metabolite. Recombinant CYP4F2, but not other major human liver CYP isoforms (including CYP3A4 and 3A7), exhibited tocopherol-ω-hydroxylase activity. Liver microsomes and recombinant CYP4F2 both exhibited substrate preference for γ-TOH over α-TOH, and recent studies show that tocotrienols are catabolized more extensively than the corresponding tocopherols. Comparative rates of ω-oxidation of tocochromanols in hepatocytes are inversely related to biopotency and directly related to cytotoxicity of these substances in macrophages. The liver contains a cytochrome P 450-mediated pathway that preferentially catabolizes "non-α" tocochromanols to excretable metabolites. This metabolic pathway appears central to the optimization of tissue tocochromanol status.

OSC.G 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 17 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2004:792821 CAPLUS

DN 141:326867

TI Human hepatocytes in primary culture: The choice to investigate drug metabolism in man

AU Gomez-Lechon, M. J.; Donato, M. T.; Castell, J. V.; Jover, R.

CS Centro de Investigacion, Hospital La Fe, Valencia, 46009, Spain

SO Current Drug Metabolism (2004), 5(5), 443-462
CODEN: CDMUBU; ISSN: 1389-2002

PB Bentham Science Publishers Ltd.

DT Journal; General Review

LA English

AB A review. Different types of hepatic tissue, including whole or split livers from organ donors or waste liver from therapeutic liver resections, are used to prepare human hepatocyte cultures. Characteristics of liver samples from different origins (gender, age, healthy/pathol. status,

xenobiotic treatment) as sources of human hepatocytes are key factors
which notably determine viability and functionality of hepatocytes. The
characterization of the CYP system can be assessed in terms of
activity (using specific substrates/inhibitors), protein (antibody anal.),
and mol. biol.-based mRNA amplification techniques (PCR technol. and DNA
microarrays). It could reasonably be considered that human hepatocytes
reflect the heterogeneity of CYP expression in human liver and
is a suitable model for drug metabolism studies. Several key issues need to
be addressed at the early stages of drug development to better select drug
candidates (metabolic profile and rate, identification of CYPs involved,
drug-drug interactions due to enzyme induction/inhibition). The metabolic
stability and metabolite profile of new chems. can be easily investigated
by incubating the drugs with fully competent metabolic models like
hepatocyte suspensions or 24-h-cultured hepatocytes. CYP
inhibitory effects are usually screened in recombinant
CYP enzymes or microsomes; however, the actual concentration of substrate
and inhibitor available to the CYP enzyme depends on processes
missing in subcellular models (transport mechanisms, cytosolic enzymes,
binding to intracellular proteins). Since intact cells more closely
reflect the environment to which drugs are exposed in the liver, cultured
hepatocytes constitute a more predictive model for drug-drug interactions.
Screening of CYP inducers cannot be done in microsomes as it
requires a cellular system fully capable of expressing CYP
genes. Primary hepatocytes are still the unique in vitro model for global
examination of the inductive potential of drugs (monitored as increases in mRNA
content or activity).
OSC.G 56 THERE ARE 56 CAPLUS RECORDS THAT CITE THIS RECORD (57 CITINGS)
RE.CNT 184 THERE ARE 184 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2004:461476 CAPLUS
DN 141:46725

TI Involvement of cytochrome P450 1A in sanguinarine detoxication
AU Vrba, Jiri; Kosina, Pavel; Ulrichova, Jitka; Modriansky, Martin
CS Institute of Medical Chemistry and Biochemistry, Faculty of Medicine,
Palacky University, Olomouc, 775 15, Czech Rep.
SO Toxicology Letters (2004), 151(2), 375-387
CODEN: TOLED5; ISSN: 0378-4274
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB Sanguinarine (SA), a member of the benzo[c]phenanthridine alkaloids, is a
potent anti-microbial agent with anti-inflammatory and anti-neoplastic
properties. However, toxicity of the alkaloid severely limits its medical
applications. Recent report by Williams et al. [Vet. Hum. Toxicol. 42
(2000) 196] implicated rat hepatic cytochrome P 450 (CYP) 1A2 as
a likely modulator of SA toxicity. Indeed, the in vitro toxicity of SA in
primary culture of rat hepatocytes and human hepatic cell line HepG2,
demonstrated as lactate dehydrogenase leakage and metabolic capability
(MTT assay), was diminished following induction of CYP1A by
2,3,7,8-tetrachlorodibenzo-p-dioxin, 3-methylcholanthrene, and
β-naphtoflavone. Using microsomes containing recombinant
CYP1A1 or CYP1A2 we show that SA causes non-competitive inhibition of the
former and competitive inhibition of the latter as assessed by
ethoxyresorufin de-ethylation (EROD). In human hepatic microsomes SA
exhibits competitive inhibition of EROD activity with apparent Ki of 2
μM, a value identical to that observed for CYP1A2 inhibition in
recombinant system. Pre-incubation of SA with human liver
microsomes resulted in time-dependent, but not dose-dependent decline in
EROD activity suggesting CYP1A2 inhibition is not mechanism based. SA
also inhibits activity of NADPH:CYP reductase, an enzyme
required for CYP activity, with IC50 very similar to that observed
for EROD inhibition. Tentative mechanism for CYP1A involvement in
decreased in vitro SA toxicity is discussed.
OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2004:379281 CAPLUS
DN 141:48385
TI Role of hepatocyte nuclear factor 3γ in the expression of human CYP2C genes
AU Bort, Roque; Gomez-Lechon, M. Jose; Castell, Jose V.; Jover, Ramiro
CS Centro de Investigacion, Unidad de Hepatologia Experimental, Hospital Universitario La Fe, Valencia, E-46009, Spain
SO Archives of Biochemistry and Biophysics (2004), 426(1), 63-72
CODEN: ABBIA4; ISSN: 0003-9861
PB Elsevier Science
DT Journal
LA English
AB Hepatocyte nuclear factor 3γ (HNF-3γ) is an important transcription factor for the maintenance of specific liver functions. However, its relevance in the expression of human cytochrome P 450 (CYP) genes has not yet been explored. Several HNF3 putative binding sites can be identified in human CYP2C 5'-flanking regions. Gene reporter expts. with proximal promoters revealed that HNF-3γ transactivated CYP2C8, CYP2C9, and CYP2C19 (25-, 4-, and 4-fold, resp.), but it did not trans-activate CYP2C18. However, overexpression of HNF-3γ in hepatoma cells by means of a recombinant adenovirus induced CYP2C9, CYP2C18, and CYP2C19 mRNA (4.5-, 20-, and 50-fold, resp.) but did not activate endogenous CYP2C8. The lack of effect of HNF-3γ on endogenous CYP2C8 could be reversed by treating cells with the deacetylase inhibitor, trichostatin A, suggesting the existence of chromatin condensation around functional HNF3 elements in this gene. Thus, HNF3γ is an important transcription factor for the hepatic-specific expression of human CYP2C genes. The results also evidence that efficient transfection tools, such as adenoviral vectors, may be decisive for assessing the role of transcription factor on chromatin organized genes.
OSC.G 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2004:6792 CAPLUS
DN 141:66576
TI Metabolism of Indirubin and indigo, endogenous aryl hydrocarbon receptor

ligand candidates, and competitive effect with respect to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
AU Sugihara, Kazumi; Kitamura, Shigeyuki; Okayama, Takashige; Kohno, Youichi; Ohta, Shigeru; Yamashita, Keisuke; Okamura, Saori; Yasuda, Mineo; Saeki, Ken'ich; Matsui, Saburo; Matsuda, Tomonari
CS Graduate School of Biomedical Sciences, Hiroshima University, Japan
SO Organohalogen Compounds (2003), 65, 134-137
CODEN: ORCOEP; ISSN: 1026-4892
PB International Symposium on Halogenated Environmental Organic Pollutants and Persistent Organic Pollutants, Inc.
DT Journal
LA English
AB Aryl hydrocarbon receptor (AhR) is a ligand-binding transcription factor which was isolated as a 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) receptor in the cell, but remains an orphan receptor. Indirubin and indigo were identified as AhR ligands in human urine and serum by means of a recombinant yeast assay. The metabolism and excretion of Indirubin, indigo, and Indigocarmine were examined in rats and mice. It was demonstrated that Indirubin and indigo are easily metabolized and excreted in vivo. A competitive effect of Indirubin with respect to TCDD or MC in vivo and in vitro was observed The induction of liver CYP activities by Indirubin was lower than that of TCDD and Indirubin did not affect the inducing effect of TCDD. Indirubin was metabolized by liver microsomal CYP1A1/2, and reductive metabolism was catalyzed by cytosolic enzymes.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2003:625209 CAPLUS
DN 140:12327
TI Human hepatocytes as a tool for studying toxicity and drug metabolism
AU Gomez-Lechon, M. J.; Donato, M. T.; Castell, J. V.; Jover, R.
CS Centro de Investigacion, Hospital La Fe, Valencia, 46009, Spain
SO Current Drug Metabolism (2003), 4(4), 292-312
CODEN: CDMUBU; ISSN: 1389-2002
PB Bentham Science Publishers Ltd.

DT Journal; General Review
LA English
AB A review. Drugs are usually biotransformed into new chemical species that may have either toxic or therapeutic effects. Drug metabolism studies are routinely performed in laboratory animals but, due to metabolic interspecies differences when compared to man, they are not accurate enough to anticipate the metabolic profile of a drug in humans. Human hepatocytes in primary culture provide the closest in vitro model to human liver and the only model that can produce a metabolic profile of a given drug that is very similar to that found in vivo. However their availability is limited due to the restricted access to suitable tissue samples. The scarcity of human liver has led to optimizing the cryopreservation of adult hepatocytes for long-term storage and regular supply. Human hepatocytes in primary culture express typical hepatic functions and express drug metabolizing enzymes. Moreover, qual. and quant. similarities between in vitro and in vivo metabolism of drugs were observed Different strategies have been envisaged to prolong cell survival and delay the spontaneous decay of the differentiated phenotype during culture. Thus, hepatocytes represent the most appropriate model for the evaluation of integrated drug metabolism, toxicity/metabolism correlations, mechanisms of hepatotoxicity, and the interactions (inhibition and induction) of xenobiotics and drug-metabolizing enzymes. However, in view of limitations of primary hepatocytes, efforts are made to develop alternative cellular models (i.e. metabolic competent CYP -engineered cells stably expressing individual CYPs and transient expression of CYPs by transduction of hepatoma cells with recombinant adenoviruses). In summary, several cellular tools are available to address key issues at the earliest stages of drug development for a better candidate selection and hepatotoxicity risk assessment.
OSC.G 60 THERE ARE 60 CAPLUS RECORDS THAT CITE THIS RECORD (61 CITINGS)

RE.CNT 179 THERE ARE 179 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2003:364949 CAPLUS
DN 139:271844
TI Interplay between transcriptional and post-transcriptional regulation of
Cyp2a5 expression
AU Glisovic, Tina; Soderberg, Malin; Christian, Kyle; Lang, Matti; Raffalli-Mathieu, Francoise
CS Uppsala Biomedical Centre, Division of Pharmaceutical Biochemistry,
Uppsala University, Uppsala, SE-751 23, Swed.
SO Biochemical Pharmacology (2003), 65(10), 1653-1661
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB The cytochrome P 450 (Cyp) 2a5 gene can be upregulated transcriptionally or by mRNA stabilization. The heterogeneous nuclear ribonucleoprotein (hnRNP) A1 interacting with the CYP2A5 mRNA has been shown to be a key post-transcriptional regulator of the Cyp2a5 gene. The aim of this study was to investigate if the transcriptional and post-transcriptional steps of Cyp2a5 expression are linked. This was done by modifying the transcription rate with transcriptional inducers (phenobarbital and cAMP) and inhibitors (actinomycin D and 5,6-dichloro-1-beta-d-ribofuranosylbenzimidazole) and analyzing the effects upon post-transcriptional events. We found that inhibition of transcription led to relocalization of hnRNP A1 from the nucleus to the cytoplasm, to its strongly increased binding to the cytoplasmic CYP2A5 mRNA and to CYP2A5 mRNA stabilization. In contrast, stimulated transcription resulted in increased binding of nuclear hnRNP A1 to the Cyp2a5 promoter, and overexpression of hnRNP A1 led to stimulated transcription of a Cyp2a5 promoter-driven luciferase recombinant . This strongly suggests that the transcriptional and post-transcriptional stages of Cyp2a5 expression are interrelated and that the nucleocytoplasmic shuttling hnRNP A1 may coordinate these different steps.
OSC.G 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2002:706086 CAPLUS
DN 138:84120
TI Improvement in the differentiated hepatic phenotype of immortalized human
hepatocytes by adenovirus mediated p21 gene transfer
AU Kobayashi, Naoya; Sakaguchi, Masakiyo; Okitsu, Teru; Totsugawa, Toshinori;
Maruyama, Masanobu; Matsumura, Toshihisa; Watanabe, Takamasa; Noguchi,
Hirofumi; Kosaka, Yoshikazu; Fujiwara, Toshiyoshi; Tanaka, Noriaki
CS Department of Surgery, Okayama University Graduate School of Medicine and
Dentistry, Okayama, 700-8558, Japan
SO ASAIO Journal (2002), 48(4), 355-359
CODEN: AJOUET; ISSN: 1058-2916
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The p21 mol., a potent cyclin dependent kinase inhibitor, regulates the
transition from the G1 phase to the S phase of the cell cycle and is
involved in terminal cellular differentiation. The overexpression of p21
has been shown to induce differentiation in various cell lines. We have
made an effort to establish a reliable human hepatocyte cell
line as a source of hepatic function in bioartificial liver (BAL) therapy.
In this work, we investigated the effect of p21 on the differential
phenotype of simian virus 40 large T antigen (SV40Tag) immortalized human
hepatocytic NKNT-3 cells. A recombinant adenoviral vector
expressing a p21 gene under control of the cytomegalovirus (CMV) promoter
(Ad-p21) was used to efficiently transfer genes into NKNT-3 cells. The
morphol. alterations, the cell cycle progression, and the expression of P
450 associated enzymes (CYPs) were carefully examined in NKNT-3 cells that had
been infected with Ad-p21. Adenovirus mediated gene delivery of p21 was
efficiently achieved in NKNT-3 cells without affecting cellular structure.
After Ad-p21 infection, NKNT-3 cells were G0/G1 arrested in cell cycle

anal. NKNT-3 cells that had been infected with Ad-p21 showed differentiated hepatic phenotypes in morphol. and improvement in protein expression of CYP 3A4 and CYP 2C9. In the present work, we demonstrate that the exogenous expression of p21 enhances the differential phenotype of immortalized hepatocytic NKNT-3 cells.
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2001:580723 CAPLUS
DN 135:352309
TI Carbamazepine: a "blind" assessment of CYP-associated metabolism and interactions in human liver-derived in vitro systems
AU Pelkonen, O.; Myllynen, P.; Taavitsainen, P.; Boobis, A. R.; Watts, P.; Lake, B. G.; Price, R. J.; Renwick, A. B.; Gomez-Lechon, M.-J.; Castell, J. V.; Ingelman-Sundberg, M.; Hidestrand, M.; Guillouzo, A.; Corcos, L.; Goldfarb, P. S.; Lewis, D. F. V.
CS Department of Pharmacology and Toxicology, University of Oulu, Oulu, FIN-90014, Finland
SO Xenobiotica (2001), 31(6), 321-343
CODEN: XENOBH; ISSN: 0049-8254
PB Taylor & Francis Ltd.
DT Journal
LA English
AB The ability of various in vitro systems for CYP enzymes (computer modeling, human liver microsomes, precision-cut liver slices, hepatocytes in culture, recombinant enzymes) to predict various aspects of in vivo metabolism and kinetics of carbamazepine (CBZ) was investigated. The study was part of the EUROCYP project that aimed to evaluate relevant human in vitro systems to study drug metabolism CBZ was given to the participating labs. without disclosing its chemical nature. The most important enzyme (CYP3A4) and metabolic route (10,11-epoxidn.) were predicted by all the systems studied. Minor enzymes and routes were predicted to a different extent by various systems. Prediction of a clearance class, i.e. slow clearance, was correctly predicted by microsomes, slices, hepatocytes and recombinant enzymes (CYP3A4). The 10,11-epoxidn. of CBZ by the recombinant CYP3A4 was enhanced by the addition of exogenous cytochrome-bs, leading to a

considerable over-prediction. Induction potency of CBZ was predicted in cultured hepatocytes in which 7-ethoxycoumarin O-deethylase was used as an index activity. It seems that for a principally CYP-metabolized substance such as CBZ, all liver-derived systems provide useful information for prediction of metabolic routes, rates and interactions.
OSC.G 33 THERE ARE 33 CAPLUS RECORDS THAT CITE THIS RECORD (33 CITINGS)
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 25 OF 28 EMBASE
AN 2000305019 EMBASE
TI Cytochrome P450 3A4-mediated interaction of diclofenac and quinidine.
AU Ngui, J.S.; Tang, W., Dr. (correspondence); Stearns, R.A.; Shou, M.; Miller, R.R.; Zang, Y.; Lin, J.H.; Baillie, T.A.
CS Department of Drug Metabolism, Merck and Co., PO Box 2000, Rahway, NJ 07065, United States.
SO Drug Metabolism and Disposition, (2000) Vol. 28, No. 9, pp. 1043-1050.
Refs: 32
ISSN: 0090-9556 CODEN: DMDSAI
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 14 Sep 2000
Last Updated on STN: 14 Sep 2000
AB The metabolism of diclofenac to its 5-hydroxylated derivative in humans is catalyzed by cytochrome P450 (CYP)3A4. We report herein that in vitro this biotransformation pathway is stimulated by quinidine. When diclofenac was incubated with human liver microsomes in the presence of quinidine, the formation of 5-hydroxydiclofenac increased 6-fold relative to controls. Similar phenomena were observed with diastereoisomers of quinidine, including quinine and the threo epimers, which produced an enhancement in the formation of 5-hydroxydiclofenac in the order of 6- to

9-fold. This stimulation of diclofenac metabolism was diminished when human liver microsomes were pretreated with a monoclonal inhibitory antibody against CYP3A4. In contrast, neither cytochrome b(5) nor CYP oxidoreductase appeared to mediate the stimulation of diclofenac metabolism by quinidine, suggesting that the effect of quinidine is mediated through CYP3A4 protein. Further kinetic analyses indicated that V(max) values for the conversion of diclofenac to its 5-hydroxy derivative increased 4.5-fold from 13.2 to 57.6 nmol/min/nmol of CYP with little change in K(m) (71-56 μM) over a quinidine concentration range of 0 to 30 μM. Conversely, the metabolism of quinidine was not affected by the presence of diclofenac; the K(m) value estimated for the formation of 3-hydroxyquinidine was 1.5 μM, similar to the quinidine concentration required to produce 50% of the maximum stimulatory effect on diclofenac metabolism. It appears that the enhancement of diclofenac metabolism does not interfere with quinidine's access to the ferriheme-oxygen complex, implicating the presence of both compounds in the active site of CYP3A4 at the same time. Finally, a 4-fold increase in 5-hydroxydiclofenac formation was observed in human hepatocyte suspensions containing diclofenac and quinidine, demonstrating that this type of drug-drug interaction occurs in intact cells.

L6 ANSWER 26 OF 28 EMBASE
AN 1996144716 EMBASE
TI Role of nitric oxide in the cytokine-mediated regulation of cytochrome P-450.
AU Carlson, T.J.; Billings, R.E., Dr. (correspondence)
CS Department of Environmental Health, CVMBS, Colorado State University, Fort Collins, CO 80523, United States.
SO Molecular Pharmacology, (1996) Vol. 49, No. 5, pp. 796-801.
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article

FS 026 Immunology, Serology and Transplantation
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 4 Jun 1996
Last Updated on STN: 4 Jun 1996
AB We explored the effects of cytokines on cytochrome P-450 (CYP) in rat hepatocyte primary cultures. CYP content and several CYP protein levels were assessed in hepatocytes treated with a cytokine combination consisting of tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), and interferon- γ (IFNγ). The combination was found to depress CYP content by 69 ± 6%. Protein levels of CYP forms 1A2, 2C11, 2B1/2, and 3A2 were assessed with immunoblotting. Treatment with the cytokine combination resulted in a decrease in each CYP enzyme, with CYP2B1/2 exhibiting the greatest loss, to 33 ± 9% of untreated cells. The addition of inhibitors of nitric oxide synthase (NOS) significantly prevented the cytokine-mediated decrease in each CYP protein, indicating a role for nitric oxide (NO) in the down-regulation. Treatment of hepatocytes with the NO donor 1-hydroxy-2-oxo-3,3-bis(3-aminoethyl)-1-triazene (300 μM) caused a decrease in each CYP apoprotein, with CYP2B1/2 exhibiting the greatest decrease, to 33 ± 8% of untreated cells. Decreases in GYP protein levels were observed in response to treatment with TNFα, IL-1β, or IL-6 alone. With IL-1β treatment, increased levels of NO production were accompanied by decreased levels of each CYP protein. With TNFα treatment, increased levels of NO production were accompanied by decreased levels of CYP2B1/2 and CYP3A2. The effects of IL-1β and TNFα were blocked by the inclusion of the NOS inhibitors. Conversely, IL-6 caused a decrease in each of the CYP enzymes but did not affect NO production. The results indicate a dissociation in vitro between NOS induction and CYP down- regulation for IL-6 treatment, whereas the down-regulation of CYP by TNFα and IL-1β in vitro is directly associated with NO production.

L6 ANSWER 27 OF 28 EMBASE
AN 1995281059 EMBASE
TI Induction of cytochrome P-4502B1-related mouse cytochrome P450 and

regulation of its expression by epidermal growth factor/transforming growth factor α in primary hepatocyte culture.
AU Aubrecht, J.; Hirsch-Ernst, K.I. (correspondence); Becker-Rabbenstein, V.; Kahl, G.F.; Taniguchi, H.; Hohne, M.W.
CS Inst. of Pharmacology and Toxicology, University of Gottingen, Robert-Koch-Strasse 40, D-37075 Gottingen, Germany.
SO Biochemical Pharmacology, (1995) Vol. 50, No. 6, pp. 781-785. ISSN: 0006-2952 CODEN: BCPCA6
CY United Kingdom
DT Journal; Article
FS 016 Cancer
022 Human Genetics
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
ED Entered STN: 17 Oct 1995
Last Updated on STN: 17 Oct 1995
AB Phenobarbital-dependent induction of mouse cytochrome P-450 (Cyp) orthologous to rat CYP2B1 and its modulation by hepatotrophic growth factors were examined in primary hepatocyte cultures. Compared to rat hepatocytes, induction in mouse hepatocytes was more rapid and effective. Ligands of the EGF receptor, epidermal growth factor, and transforming growth factor α inhibited induction on the basis of protein expression and CYP2B-associated 7-pentoxyresorufin-O-depentylase activity. Furthermore, EGF led to repression of accumulation of corresponding mRNA under phenobarbital, an effect not blocked by inhibition of protein synthesis under cycloheximide. Ligands of the EGF receptor may contribute towards the decrease in hepatic CYP expression observed during (pre)neoplastic development and regeneration.

L6 ANSWER 28 OF 28 EMBASE
AN 1995150354 EMBASE
TI Suppression of the constitutive expression of cytochrome P-450 2C11 by cytokines and interferons in primary cultures of rat hepatocytes: Comparison with induction of acute-phase genes and demonstration that CYP2C11 promoter sequences are involved in the suppressive response to

interleukins 1 and 6.
AU Chen, J.-Q.; Strom, A.; Gustafsson, J.-A.; Morgan, E.T. (correspondence)
CS Department of Pharmacology, 5119 Rollins Research Center, Emory University, Atlanta, GA 30322, United States.
SO Molecular Pharmacology, (1995) Vol. 47, No. 5, pp. 940-947.
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered STN: 7 Jun 1995
Last Updated on STN: 7 Jun 1995
AB Hepatic expression of various members of the cytochrome P-450 (CYP
) superfamily is suppressed during inflammatory responses. We have shown
that the specific expression of P-450 2C11 in male rat liver is suppressed
transcriptionally by endotoxin treatment. To investigate the molecular
mechanisms underlying this phenomenon, we studied the effects of the
inflammatory cytokines interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF), interferon (IFN)-α, and IFN-γ on the
expression of P-450 2C11 and the mRNAs of two typical acute-phase protein
genes, α(1)-acid glycoprotein (AGP) and fibrinogen, in primary hepatocyte cultures. IL-1, IL-6, TNF, and IFN-α all
suppressed P-450 2C11 mRNA, whereas IFN-γ had no effect. IL-1 and
TNF were more effective than IL-6 in the suppression of P-450 2C11 mRNA.
Whereas IL-1 and IL-6 effects on P-450 2C11 were accompanied by induction
of AGP and fibrinogen mRNAs, IFN-α and TNF treatments had no effect
on AGP. The suppression of P-450 2C11 and the induction of AGP by IL-1
showed similar time courses. The combination of IL-1 and IL-6 showed
additivity in suppression of P-450 2C11, at maximally effective
concentrations of cytokines. The effects of IL-1 on P-450 2C11 and AGP
expression were blocked by IL-1 receptor antagonist protein. We also
studied the effects of IL-1 and IL-6 on the transient expression of

chloramphenicol acetyltransferase reporter gene constructs containing 200
or 1287 base pairs of the 5' flanking region of the CYP2C11 gene, transfected into primary hepatocytes. The chloramphenicol acetyltransferase activities in cells transfected with the 200-base pair
construct were reduced to about 33% and 58% of control levels by treatment
with IL-1 or IL-6, respectively, suggesting that sequences important for
cytokine down-regulation lie within the proximal promoter region of the
CYP2C11 gene.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	111.74	124.77

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-7.38	-7.38

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=> FIL BIOSIS CAPLUS EMBASE

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FULL ESTIMATED COST	0.63	125.40

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-7.38

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=> d his

     (FILE 'HOME' ENTERED AT 18:26:36 ON 19 AUG 2009)

     FILE 'BIOSIS, CAPLUS, EMBASE' ENTERED AT 18:26:44 ON 19 AUG 2009
L1             3 S CYP (3A) ENGINEERED CELL
L2             1 DUP REM L1 (2 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 18:28:07 ON 19 AUG 2009

     FILE 'BIOSIS, CAPLUS, EMBASE' ENTERED AT 18:30:42 ON 19 AUG 2009
L3          5627 S HEPATOCYTE AND RECOMBIN?
L4            81 S L3 AND CYP
L5            51 DUP REM L4 (30 DUPLICATES REMOVED)
L6            28 S L5 AND PY<=2004

     FILE 'STNGUIDE' ENTERED AT 18:43:35 ON 19 AUG 2009

     FILE 'BIOSIS, CAPLUS, EMBASE' ENTERED AT 18:49:12 ON 19 AUG 2009

=> s hepatocyte (s) (transfect? or transform? or transdu?)
L7         5849 HEPATOCYTE (S) (TRANSFECT? OR TRANSFORM? OR TRANSDU?)

=> s adenovir? and hepatocyt?
L8         3547 ADENOVIR? AND HEPATOCYT?

=> s l7 or l8
L9         9068 L7 OR L8

=> s l9 and cyp
L10          70 L9 AND CYP

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11           40 DUP REM L10 (30 DUPLICATES REMOVED)

=> d bib abs 1-
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L11  ANSWER 1 OF 40  EMBASE  COPYRIGHT (c) 2009 Elsevier B.V. All
rights
     reserved on STN
AN   2009271551  EMBASE
TI   Coordinate regulation of metabolic enzymes and transporters by
nuclear
     transcription factors in human liver disease.
AU   Desmond, Paul V.
CS   St. Vincent's Hospital Melbourne, PO Box 2900, Fitzroy, VIC 3065,
     Australia. paul.desmond@svhm.org.au
AU   Congiu, Mario; Mashford, Maurice L.; Desmond, Paul V.
CS   Department of Gastroenterology, St. Vincent's Hospital Melbourne,
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AU Congiu, Mario; Desmond, Paul V.
CS University of Melbourne, Department of Medicine, St. Vincent's Hospital
Melbourne, Melbourne, VIC, Australia. paul.desmond@svhm.org.au
AU Slavin, John L.
CS Department of Pathology, St. Vincent's Hospital Melbourne, Melbourne, VIC,
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AU Desmond, P. V., Prof. (correspondence)
CS St. Vincent's Hospital Melbourne, PO Box 2900, Fitzroy, VIC 3065,
Australia. paul.desmond@svhm.org.au
SO Journal of Gastroenterology and Hepatology, (June 2009) Vol. 24, No. 6,
pp. 1038-1044.
Refs: 39
ISSN: 0815-9319 E-ISSN: 1440-1746 CODEN: JGHEEO
PB Blackwell Publishing, 550 Swanston Street, Carlton South, VIC 3053,
Australia.
CY Australia
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
048 Gastroenterology
LA English
SL English
ED Entered STN: 23 Jun 2009
Last Updated on STN: 23 Jun 2009
AB Background: It has been hypothesised, mainly from studies with animal
models of liver disease, that the transport of substrates for metabolic
enzymes and their subsequent metabolism and elimination in hepatic bile or
blood is co-ordinated, but there is little information on this process in
diseased human liver. Methods: In this study we have measured by reverse
transcription polymerase chain reaction (RT-PCR) major genes involved in
drug metabolism from UDP-glucuronosyltransferases (UGT1A1, UGT1A6, UGT1A9,
and UGT2B4) and cytochrome P450 (CYP) families (CYP1A2, CYP2C9,
CYP2C19, CYP2D6, CYP2E1, and CYP3A4), transport (OATP-C, MRP2, MRP3, and
MDR1) and major transcription factors (PXR, CAR, HNF1alpha, HNF4alpha,
RXR, and AHR) involved in their regulation. Liver biopsy tissue from
patients with viral hepatitis was scored for inflammation and fibrosis by
the METAVIR system, and separated into groups with mild (A0-1; F0-1, n =

20) or severe (A2-3; F3-4, n = 19) liver disease. Correlation analysis (Spearman rank-test, P < 0.05) was used to identify metabolic enzymes and transporters which shared significant correlation with transcription factors. Results: Our results show an extensive correlation between transcription factors, transporters, and metabolic enzymes. An unexpected finding was that this was substantially greater in the severely diseased liver. Cross-talk between transcription factors was markedly increased in tissue from patients with severe liver disease, particularly between CAR, HNF4alpha, and PXR. Conclusion: Our results support the hypothesis of co-ordinate regulation of metabolic enzymes and transporters in diseased human liver, as part of a widespread co-ordinated process under the control of nuclear receptor transcription factors. .COPYRGT. 2009 The Authors. Journal compilation .COPYRGT. 2009 Journal of Gastroenterology and Hepatology Foundation and Blackwell Publishing Asia Pty Ltd.

L11 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2008:1294154 CAPLUS
DN 150:389308
TI Effect of berberine on hepatocyte proliferation, inducible nitric oxide synthase expression, cytochrome P450 2E1 and 1A2 activities in diethylnitrosamine- and phenobarbital-treated rats
AU Zhao, Xuan; Zhang, Jun-Jie; Wang, Xin; Bu, Xiu-Yun; Lou, Ya-Qing; Zhang, Guo-Liang
CS Department of Pharmacology, Basic Medical School, Beijing University, Beijing, 100083, Peop. Rep. China
SO Biomedicine & Pharmacotherapy (2008), 62(9), 567-572
CODEN: BIPHEX; ISSN: 0753-3322
PB Elsevier Masson SAS
DT Journal
LA English
AB This study investigated the effect of berberine on the early phase of hepatocarcinogenesis stimulated by diethylnitrosamine (DEN, 150 mg/kg, 4 wk) plus phenobarbital (PB, 75 mg/kg, 7 days) in rats. The expressions of

proliferating cell nuclear antigen (PCNA) and inducible nitric oxide synthase (iNOS) were evaluated by immunohistochem. The activities of CYP isoenzymes were analyzed using different probe drugs including chlorzoxazone (CYP2E1) and phenacetin (CYP1A2) by high-performance liquid chromatog. (HPLC) in vivo or in vitro. Results showed that the expressions of PCNA and iNOS were induced by DEN plus PB in liver tissues. Oral administration of berberine (50 mg/kg) inhibited the hepatocyte proliferation and iNOS expression, decreased cytochrome P 450 content, inhibited activities of CYP2E1 and CYP1A2 in DEN-plus-PB-treated rats in vivo. Moreover, berberine (10, 50 and 100 μM) inhibited the activities of CYP2E1 and CYP1A2 in microsomes isolated from DEN-plus-PB-treated rats in vitro, suggesting that anti-hepatocarcinogenetic potential of berberine might be due to inhibiting oxidative metabolic activities of CYP 2E1 and CYP1A2, and decreasing NO production in rats.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
DUPLICATE 1
AN 2008:677033 BIOSIS
DN PREV200800677032
TI Coactivator PGC-1 alpha regulates the fasting inducible xenobiotic-metabolizing enzyme CYP2A5 in mouse primary hepatocytes
.
AU Arpiainen, Satu; Jarvenpaa, Sanna-Mari; Manninen, Aki; Viitala, Pirkko; Lang, Matti A.; Pelkonen, Olavi; Hakkola, Jukka [Reprint Author]
CS Univ Oulu, Dept Pharmacol and Toxicol, POB 5000,Aapistie 5B, Oulu 90014, Finland
jukka.hakkola@oulu.fi
SO Toxicology and Applied Pharmacology, (OCT 1 2008) Vol. 232, No. 1, pp. 135-141.
CODEN: TXAPA9. ISSN: 0041-008X.
DT Article
LA English
ED Entered STN: 27 Nov 2008
Last Updated on STN: 27 Nov 2008

AB The nutritional state of organisms and energy balance related diseases such as diabetes regulate the metabolism of xenobiotics such as drugs, toxins and carcinogens. However, the mechanisms behind this regulation are mostly unknown. The xenobiotic-metabolizing cytochrome P450 (CYP) 2A5 enzyme has been shown to be induced by fasting and by glucagon and cyclic AMP (cAMP), which mediate numerous fasting responses. Peroxisome proliferator-activated receptor gamma coactivator (PGC)-1 alpha triggers many of the important hepatic fasting effects in response to elevated cAMP levels. In the present study, we were able to show that cAMP causes a coordinated induction of PGC-1 alpha expression level by adenovirus mediated gene transfer increased CYP2A5 transcription, Co-transfection of Cyp2a5' promoter constructs with PGC-1 alpha expression vector demonstrated that PGC-1 alpha is able to activate Cyp2a5 transcription through the hepatocyte nuclear factor (HNF)-4 alpha response element in the proximal promoter of the Cyp2a5 gene. Chromartin immunoprecipitation assays showed that PGC-1 alpha binds, together with HNF-4 alpha, to the same region at the Cyp2a5 proximal promoter. In conclusion, PGC-1 alpha mediates the expression of Cyp2A5 induced by cAMP in mouise hepatocytes throuch coactivation of transcription factor HNF-4 alpha. This strongly suggests that PGC-1 alpha is the major factor mediating the fasting response of CYP2A5.

L11 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2008:691297 CAPLUS
DN 149:217282
TI Evidence that the Anticarcinogenic Effect of Caffeic Acid Phenethyl Ester in the Resistant Hepatocyte Model Involves Modifications of Cytochrome P450
AU Beltran-Ramirez, Olga; Aleman-Lazarini, Leticia; Salcido-Neyoy, Martha; Hernandez-Garcia, Sergio; Fattel-Fazenda, Samia; Arce-Popoca, Evelia; Arellanes-Robledo, Jaime; Garcia-Roman, Rebeca; Vazquez-Vazquez, Patricia;

Sierra-Santoyo, Adolfo; Villa-Trevino, Saul
CS Departamento de Biologia Celular, Centro de Investigacion y de Estudios
Avanzados del Instituto Politecnico Nacional (CINVESTAV), Mexico City,
07360, Mex.
SO Toxicological Sciences (2008), 104(1), 100-106
CODEN: TOSCF2; ISSN: 1096-6080
PB Oxford University Press
DT Journal
LA English
AB Caffeic acid phenethyl ester (CAPE), a natural component of propolis,
shows anticarcinogenic properties in the modified resistant hepatocyte
model when administered before initiation or promotion of
hepatocarcinogenesis process; however, information about the mechanism
underlying this chemoprotection is limited. The aim of this work was to
characterize the effect of CAPE on cytochrome P 450 (CYP), which
is involved in diethylnitrosamine (DEN) metabolism during the initiation stage
of chemical hepatocarcinogenesis. Male Fischer-344 rats were treated as in
the modified resistant hepatocyte model. Liver samples were obtained at
four different times: at 12 h after pretreatment with CAPE and at 12 and
24 h and 25 days after DEN administration. Liver damage was determined by
histol. with hematoxylin and eosin, measurement of total CYP
levels and enzyme activity, and γ-glutamyl transpeptidase-pos.
(GGT+) staining of hepatocyte foci. CAPE administration prevented
DEN-induced necrosis at 24 h. It also decreased O-dealkylation of
7-ethoxy-resorufin (EROD), O-dealkylation of 7-methoxyresorufin (MROD),
and 7-pentoxy-resorufin activities at 12 h after its administration and
EROD and MROD activities at 12 h after administration of DEN. CAPE
treatment decreased GGT+ foci by 59% on day 25. Our results suggest that
CAPE modifies the enzymic activity of CYP isoforms involved in
the activation of DEN, such as CYP1A1/2 and CYP2B1/2. These findings
describe an alternative mechanism for understanding the ability of CAPE to
protect against chemical hepatocarcinogenesis.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2008:1322498 CAPLUS
DN 150:4166
TI Molecular and macromolecular alterations of recombinant adenoviral vectors do not resolve changes in hepatic drug metabolism during infection
AU Callahan, Shellie M.; Wonganan, Piyanuch; Croyle, Maria A.
CS College of Pharmacy, Division of Pharmaceutics, The University of Texas at Austin, Austin, TX, USA
SO Virology Journal (2008), 5, No pp. given
CODEN: VJIOA4; ISSN: 1743-422X
URL: http://www.virologyj.com/content/pdf/1743-422X-5-111.pdf
PB BioMed Central Ltd.
DT Journal; (online computer file)
LA English
AB In this report we test the hypothesis that long-term virus-induced alterations in CYP occur from changes initiated by the virus that may not be related to the immune response. Enzyme activity, protein expression and mRNA and CYP3A2, a correlate of human CYP3A4, and CYP2C11, responsive to inflammatory mediators, were assessed 0.25, 1, 4, and 14 days after administration of several different recombinant adenoviruses at a dose of 5.7 + 1012 virus particles (vp)/kg to male Sprague Dawley rats. Wild type adenovirus, containing all viral genes, suppressed CYP3A2 and 2C11 activity by 37% and 39%, resp. within six hours. Levels fell to 67% (CYP3A2) and 79% (CYP2C11) of control by 14 days ($p \leq 0.01$). Helper-dependent adenovirus, with all viral genes removed, suppressed CYP3A2 (43%) and CYP2C11 (55%) within six hours. CYP3A2 remained significantly suppressed (47%, 14 days, $p \leq 0.01$) while CYP2C11 returned to baseline at this time. CYP3A2 and 2C11 were reduced by 45 and 42% resp. 6 h after treatment with PEGylated adenovirus, which has a low immunol. profile ($p \leq 0.05$). CYP3A2 remained suppressed (34%, $p \leq 0.05$) for 14 days while CYP2C11 recovered. Inactivated virus suppressed CYP3A2 activity by 25-50% for 14 days ($p \leq 0.05$). CYP2C11 was affected similar manner but recovered by day 14. Microarray and in vitro studies

suggest that changes in cellular signaling pathways initiated early in
virus infection contribute to changes in CYP.
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
DUPLICATE 2
AN 2007:350354 BIOSIS
DN PREV200700349475
TI Loss of sexually dimorphic liver gene expression upon hepatocyte-specific
deletion of Stat5a-Stat5b locus.
AU Holloway, Minita G.; Cui, Yongzhi; Laz, Ekaterina V.; Hosui, Atsushi;
Hennighausen, Lothar; Waxman, David J. [Reprint Author]
CS Boston Univ, Dept Biol, Div Cell and Mol Biol, 5 Cummington St, Boston, MA
02215 USA
djw@bu.edu
SO Endocrinology, (MAY 2007) Vol. 148, No. 5, pp. 1977-1986.
CODEN: ENDOAO. ISSN: 0013-7227.
DT Article
LA English
ED Entered STN: 13 Jun 2007
Last Updated on STN: 13 Jun 2007
AB Hepatocyte-specific, albumin-Cre recombinase-mediated deletion
of the entire mouse Stat5a-Stat5b locus was carried out to evaluate the
role of signal transducer and activator of transcription 5a and
5b (STAT5ab) in the sex-dependent transcriptional actions of GH in the
liver. The resultant hepatocyte STAT5ab-deficient mice were fertile, and
unlike global STAT5b-deficient male mice, postnatal body weight gain was
normal, despite a 50% decrease in serum IGF-I. Whole-liver STAT5ab RNA
decreased by approximately 65 - 85%, and residual STAT5 immunostaining was
observed in a minority of the hepatocytes, indicating incomplete excision
by Cre-recombinase. Quantitative PCR analysis of 20 sexually dimorphic,
liver-expressed genes revealed significant down-regulation of 10 of 11
male-specific genes in livers of male hepatocyte STAT5ab-deficient mice.
Class I female-specific liver genes were markedly up-regulated
(de-repressed), whereas the expression of class II female genes, belonging

to the Cyp3a subfamily, was unaffected by the loss of hepatocyte STAT5ab.
STAT5ab is thus required in the liver for positive regulation of male-specific genes and for negative regulation of a subset of female-specific genes. Continuous GH infusion strongly induced (> 500-fold) the class II female gene Cyp3a16 in both wild-type and hepatocyte STAT5ab-deficient male mice, indicating sex-specific transcriptional regulation by GH that is STAT5ab independent. In contrast, hepatocyte STAT5ab deficiency abolished the strong suppression of the male-specific Cyp2d9 by continuous GH seen in control mouse liver.
Analysis of global STAT5a-deficient mice indicated no essential requirement of STAT5a for expression of these sex-specific liver Cyp genes. Thus, the major loss of liver sexual dimorphism in hepatocyte STAT5ab-deficient mice can primarily be attributed to the loss of STAT5b.

L11 ANSWER 7 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
DUPLICATE 3
AN 2007:609523 BIOSIS
DN PREV200700611423
TI Examination of glucocorticoid receptor alpha-mediated transcriptional regulation of P-glycoprotein, CYP3A4, and CYP2C9 genes in placental trophoblast cell lines.
AU Pavek, P. [Reprint Author]; Cerveny, L.; Svecova, L.; Brysch, M.; Libra, A.; Vrzal, R.; Nachtigal, P.; Staud, F.; Ulrichova, J.; Fendrich, Z.; Dvorak, Z.
CS Charles Univ Prague, Fac Pharm, Dept Pharmacol and Toxicol, Heyrovskoho 1203, CS-50005 Hradec Kralove, Czech Republic
petr.pavek@faf.cuni.cz
SO Placenta, (OCT 2007) Vol. 28, No. 10, pp. 1004-1011.
CODEN: PLACDF. ISSN: 0143-4004.
DT Article
LA English
ED Entered STN: 6 Dec 2007
Last Updated on STN: 6 Dec 2007
AB The placental trophoblast at different stages of pregnancy contains some drug transporters and xenobiotic-metabolising enzymes, as well as ligand-activated nuclear receptors, which control their inducible transcriptional regulation. Glucocorticoid receptor alpha (GR alpha) is expressed in both placental syncytiotrophoblast and cytotrophoblast. GRa

was shown to control inducible expression of several enzymes of the cytochrome P-450 family (CYP) and the drug transporter P-glycoprotein in the liver. However, GR alpha-mediated transcriptional regulation of drug transporters and CYPs has not been studied in the placental trophoblast. In this study, we examined the expression and activity of GR alpha in the transcriptional regulation of P-glycoprotein, CYP3A4, and CYP2C9 in placental trophoblast cell lines. Employing RT-PCR, Western blotting, and luciferase gene reporter assay, we detected the expression and activity of GR alpha in JEG3 and BeWo cell lines. However, we observed that only MDR1 mRNA was up-regulated after treatment of placental cells with dexamethasone. Accordingly, only the promoter of the MDR1 gene was activated by dexamethasone in gene reporter assays in placental cells and the activation was abolished by RU486, an antagonist of GR alpha. CYP3A4 and CYP2C9 promoters were activated in placental cells only after co-transfection with hepatocyte nuclear factor 4 alpha (HNF4 alpha), which indicates the hepatocyte-specific character of GR alpha-mediated regulation of the genes. On the other hand, coexpression of HNF4 alpha had no effect on the activation of the MDR1 gene promoter, suggesting HNF4 alpha-independent regulation via GR alpha. We conclude that GR alpha may be involved in the transcriptional regulation of P-glycoprotein in the placental trophoblast. We also indicate that the CYP3A4 and CYP2C9 genes are not inducible through GR alpha in placental cell lines, due to the lack of HNF4 alpha expression and possibly some additional hepatocyte-specific transcriptional factors.

L11 ANSWER 8 OF 40 CAPLUS
AN 2007:1169039 CAPLUS
DN 147:481143
TI Role of human hepatocyte nuclear factor 4α in the expression of drug-metabolizing enzymes and transporters in human hepatocytes assessed by use of small interfering RNA

AU Kamiyama, Yoshiteru; Matsubara, Tsutomu; Yoshinari, Kouichi; Nagata,
Kiyoshi; Kamimura, Hidetaka; Yamazoe, Yasushi
CS Division of Drug Metabolism and Molecular Toxicology, Graduate School of
Pharmaceutical Sciences, Tohoku University, Sendai, Japan
SO Drug Metabolism and Pharmacokinetics (2007), 22(4), 287-298
CODEN: DMPRB8; ISSN: 1347-4367
PB Japanese Society for the Study of Xenobiotics
DT Journal
LA English
AB Hepatocyte nuclear factor 4α (HNF4α) is an important transcription factor in hepatic gene expression. Here, we have investigated the role of HNF4α in the expression of drug-metabolizing enzymes and transporters in human hepatocytes using an adenovirus expressing human HNF4α-small interfering RNA (hHNF4α-siRNA). The hHNF4α-siRNA effectively reduced the mRNA and nuclear protein levels of hHNF4α in a concentration-dependent manner. The hHNF4α-siRNA also decreased the mRNA levels of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A9, SULT2A1, ABCB1, ABCB11, ABCC2, OATP1B1 and OCT1, as well as those of PXR and CAR. To discern the role of these nuclear receptors, we co-infected hepatocytes with hHNF4α-siRNA and PXR- or CAR-expressing adenovirus. The hHNF4α-siRNA-induced redns. of the enzyme and transporter mRNA levels were not restored except CYP2B6 mRNA levels, which were returned to the control level by overexpressing CAR. Furthermore, although hHNF4α-siRNA did not significantly affect the fold-induction of CYP2B6, CYP2C8, CYP2C9, or CYP3A4 mRNA levels following treatment with CYP inducers, the levels in hHNF4α-suppressed cells fell significantly compared to the control. These results suggest that HNF4α plays a dominant role in the expression of drug-metabolizing enzymes and transporters in human hepatocytes, and that HNF4α expression levels is a possible determinant for interindividual variations in the expression of these enzymes and transporters.
OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 40 EMBASE

reserved on STN
AN 2007091103 EMBASE
TI Primary hepatocytes: Current understanding of the regulation of metabolic enzymes and transporter proteins, and pharmaceutical practice for the use of hepatocytes in metabolism, enzyme induction, transporter, clearance, and hepatotoxicity studies.
AU Hewitt, Nicola J. (correspondence)
CS Scientific Writing Services, Wingertstrasse, Erzhausen, Germany. nickyhewittltd@yahoo.co.uk
AU Lechon, Maria Jose Gomez
CS Unidad de Hepatologia Experimental, Centro de Investigacion, Hospital La Fe, Valencia, Spain.
AU Houston, J. Brian; Hallifax, David; Brown, Hayley S.
CS School of Pharmacy and Pharmaceutical Sciences, University of Manchester, United Kingdom.
AU Maurel, Patrick
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AU Maurel, Patrick
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AU Kenna, J. Gerald
CS Global Safety Assessment, AstraZeneca, Alderley Park, Macclesfield, Cheshire, United Kingdom.
AU Gustavsson, Lena; Lohmann, Christina
CS Discovery DMPK and BA, AstraZeneca R and D Lund, Sweden.
AU Skonberg, Christian
CS Danish University of Pharmaceutical Sciences, Department of Pharmaceutics and Analytical Chemistry, Universitetsparken, Copenhagen.
AU Guillouzo, Andre
CS INSERM Universite de Rennes, France.
AU Tuschl, Gregor
CS Department of Molecular Toxicology, Institute of Toxicology, Merck KGaA, Frankfurterstrasse, Darmstadt, Germany.
AU Li, Albert P.
CS ADMET Group LLC, Rockville, MD, United States.
AU Lecluyse, Edward
CS CellzDirect, Hillsboro Street, Pittsboro, NC, United States.
AU Groothuis, Geny M. M.
CS Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, University of Groningen, A.Deusinglaan, Groningen, Netherlands.
AU Hengstler, Jan G.
CS Centre of Toxicology, Institute of Legal Medicine, University of Leipzig, Haertelstr, Leipzig, Germany.
SO Drug Metabolism Reviews, (Jan 2007) Vol. 39, No. 1, pp. 159-234. Refs: 356

ISSN: 0360-2532 E-ISSN: 1097-9883 CODEN: DMTRAR
PUI 770421167
CY United States
DT Journal; General Review; (Review)
FS 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English
SL English
ED Entered STN: 12 Apr 2007
Last Updated on STN: 12 Apr 2007
AB This review brings you up-to-date with the hepatocyte research on: 1) in vitro-in vivo correlations of metabolism and clearance; 2) CYP enzyme induction, regulation, and cross-talk using human hepatocytes and hepatocyte-like cell lines; 3) the function and regulation of hepatic transporters and models used to elucidate their role in drug clearance; 4) mechanisms and examples of idiosyncratic and intrinsic hepatotoxicity; and 5) alternative cell systems to primary human hepatocytes. We also report pharmaceutical perspectives of these topics and compare methods and interpretations for the drug development process. Copyright .COPYRGT. Informa Healthcare.

L11 ANSWER 10 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 4
AN 2006:645139 BIOSIS
DN PREV200600640210
TI Growth hormone regulation of sex-dependent liver gene expression.
AU Waxman, David J. [Reprint Author]; O'Connor, Caitlin
CS Boston Univ, Dept Biol, Div Cell and Mol Biol, 5 Cummington St, Boston, MA 02215 USA
djw@bu.edu
SO Molecular Endocrinology, (NOV 2006) Vol. 20, No. 11, pp. 2613-2629.
CODEN: MOENEN. ISSN: 0888-8809.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 22 Nov 2006
Last Updated on STN: 22 Nov 2006
AB The liver is a primary target for the action of GH, a pituitary protein

hormone that regulates a broad range of physiological processes, including long bone growth, fatty acid oxidation, glucose uptake, and hepatic steroid and foreign compound metabolism. GH exerts sex-dependent effects on the liver in many species, with many hepatic genes, most notably genes coding for cytochrome P450 (CYP) enzymes, being transcribed in a sex-dependent manner. Sex differences in CYP expression are most striking in rats and mice (up to 500-fold male-female differences), but are also seen, albeit to a much smaller degree, in humans, where they are an important determinant of the sex dependence of hepatic drug and steroid metabolism. This article examines the mechanisms whereby GH, via its sex-dependent temporal patterns of pituitary release, activates intracellular signaling leading to the sexually dimorphic transcription of CYPs and other liver-expressed genes. Recent findings implicating the GH-regulated transcription factor STAT5b (signal transducer and activator of transcription 5b), hepatocyte nuclear factors 3 beta, 4 alpha and 6, and sex differences in DNA methylation and chromatin structure in the sex-dependent actions of GH are reviewed, and current mechanistic models are evaluated.

L11 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2006:616398 CAPLUS
DN 146:156773
TI Impact of transgene expression on drug metabolism following systemic adenoviral vector administration
AU Callahan, Shellie M.; Boquet, Michael P.; Ming, Xin; Brunner, Lane J.; Croyle, Maria A.
CS College of Pharmacy, Division of Pharmaceutics, The University of Texas at Austin, Austin, TX, 78712-1074, USA
SO Journal of Gene Medicine (2006), 8(5), 566-576
CODEN: JGMEFG; ISSN: 1099-498X
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Systemic administration of a first-generation adenovirus expressing E. coli beta-galactosidase (AdlacZ) alters expression and

function of two hepatic drug-metabolizing enzymes, cytochrome P 450 (CYP) 3A2 and 2C11, for 14 days. The objective of these studies was to determine how the transgene cassette influences CYP expression and function. Sprague-Dawley rats were given 5.7 + 1012 viral particles (vp)/kg of either: AdlacZ, Ad expressing murine erythropoietin (Epo), Ad without a transgene (Null), or phosphate-buffered saline (Vehicle). Hepatic CYP protein expression, activity, mRNA and alanine aminotransferase (ALT) levels were analyzed 0.25, 1, 4, and 14 days following a single i.v. injection. Administration of Epo did not alter CYP3A2 activity, but induced RNA levels by a factor of 2 at 4 and 14 days ($P \leq 0.01$). This vector suppressed CYP2C11 activity levels by 45% at 1 day ($P \leq 0.05$) and RNA levels throughout the study period ($P < 0.05$). The Null vector suppressed CYP3A2 activity by 36, 63, 34, and 45% at 0.25, 1, 4 and 14 days, resp. ($P \leq 0.05$). CYP2C11 activity was suppressed 1 day after administration (41%) and RNA levels were suppressed at 6 h (53%) and 1 day (36%, $P \leq 0.05$). In contrast, AdlacZ suppressed both CYP3A2 and 2C11 at all time points. The immunogenic and biol. nature of the transgene cassette can influence changes in CYP3A2, but not the 2C11 isoform. The shift in transcription and translation of protein for maintenance of physiol. homeostasis to production of viral proteins and transgene product and their associated toxicity during viral infection may explain our observations.

OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2006:711768 CAPLUS

DN 145:160119

TI Peroxisome proliferator-activated receptor (PPAR)-binding protein (PBP) but not PPAR-interacting protein (PRIP) is required for nuclear translocation of constitutive androstane receptor in mouse liver

AU Guo, Dongsheng; Sarkar, Joy; Ahmed, Mohamed R.; Viswakarma, Navin; Jia, Yuzhi; Yu, Songtao; Rao, M. Sambasiva; Reddy, Janardan K.

CS The Department of Pathology, Feinberg School of Medicine, Northwestern
University, Chicago, IL, 60611, USA
SO Biochemical and Biophysical Research Communications (2006), 347(2),
485-495
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
AB The constitutive androstane receptor (CAR) regulates transcription of
phenobarbital-inducible genes that encode xenobiotic-metabolizing enzymes
in liver. CAR is localized to the hepatocyte cytoplasm but to be functional, it translocates into the nucleus in the presence of
phenobarbital-like CAR ligands. We now demonstrate that adenovirally driven EGFP-CAR, as expected, translocates into the nucleus of normal wild-type hepatocytes following phenobarbital treatment under both in vivo and in vitro conditions. Using this approach
we investigated the role of transcription coactivators PBP and PRIP in the
translocation of EGFP-CAR into the nucleus of PBP and PRIP liver conditional null mouse hepatocytes. We show that coactivator PBP is essential for nuclear translocation of CAR but not PRIP. Adenoviral expression of both PBP and EGFP-CAR restored
phenobarbital-mediated nuclear translocation of exogenously expressed CAR
in PBP null livers in vivo and in PBP null primary hepatocytes in vitro. CAR translocation into the nucleus of PRIP null livers resulted
in the induction of CAR target genes such as CYP2B10, necessary for the
conversion of acetaminophen to its hepatotoxic intermediate metabolite,
N-acetyl-p-benzoquinone imine. As a consequence, PRIP-deficiency in liver
did not protect from acetaminophen-induced hepatic necrosis, unlike that
exerted by PBP deficiency. These results establish that transcription
coactivator PBP plays a pivotal role in nuclear localization of CAR, that
it is likely that PBP either enhances nuclear import or nuclear retention
of CAR in hepatocytes, and that PRIP is redundant for CAR function.

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2006:112718 CAPLUS
DN 144:227742
TI Preferential inducibility of CYP1A1 and CYP1A2 by TCDD: Differential
regulation in primary human hepatocytes versus transformed human cells
AU Zhang, Zhi-Yi; Pelletier, Robert D.; Wong, Y. Nancy; Sugawara, Michiko;
Zhao, Nanding; Littlefield, Bruce A.
CS Department of Drug Disposition, Eisai Research Institute, Andover, MA,
01810, USA
SO Biochemical and Biophysical Research Communications (2006), 341(2),
399-407
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
AB Cytochrome P 4501A1 (CYP1A1) induction, a marker of aryl hydrocarbon (Ah)
receptor activation, has been associated with carcinogenicity of the
environmental agent 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).
Consistently, we show that TCDD treatment led to induction of CYP1A1 in
responsive human cancer cell lines including HepG2, LS174T, and MCF-7, as
determined by Western blotting and CYP1A form-selective R-warfarin 6- and
8-hydroxylation. TCDD, however, preferably induced CYP1A2, not CYP1A1, in
primary human hepatocytes. Such CYP1A form-preferred induction at the
protein level was apparently uncorrelated with non-preferred mRNA
induction in any cells studied. Moreover, while both genes were
up-regulated by TCDD in primary hepatocytes and HepG2 cells, the induction
of CYP1A1 and CYP1A2 at the mRNA level was distinguishable, indicated by
the marked differences in activation kinetics and the response to the
protein synthesis inhibitors, anisomycin and cycloheximide. Furthermore,
formation of total benzo(a)pyrene (BaP)-DNA adducts was not altered
following BaP exposure in TCDD-treated primary hepatocytes, whereas
significantly elevated, in a CYP1A1-dependent manner, in the treated HepG2

cells. Taken together, our findings, demonstrating the complexities of
TCDD-associated human Ah receptor function and differential regulations of
CYP 1A enzymes, suggest clearly the need for caution when extrapolating data obtained in cell-based models.
OSC.G 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 14 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN
AN 2006:563836 BIOSIS
DN PREV200600568863
TI Gene expression profiling in liver and testis of rats to characterize the
toxicity of triazole fungicides.
AU Tully, Douglas B.; Bao, Wenjun; Goetz, Amber K.; Blystone, Chad R.; Ren,
Hongzu; Schmid, Judith E.; Strader, Lillian F.; Wood, Carmen R.; Best,
Deborah S.; Narotsk, Michael G.; Wolf, Douglas C.; Rockett, John C.; Dix,
David J. [Reprint Author]
CS US EPA, Off Res and Dev, Res Triangle Pk, NC 27711 USA
dix.david@epa.gov
SO Toxicology and Applied Pharmacology, (SEP 15 2006) Vol. 215, No. 3, pp.
260-273.
CODEN: TXAPA9. ISSN: 0041-008X.
DT Article
LA English
OS GenBank-NM021989; EMBL-NM021989; DDBJ-NM021989; GenBank-NM173295;
EMBL-NM173295; DDBJ-NM173295; GenBank-NM057105; EMBL-NM057105;
DDBJ-NM057105; GenBank-NM031154; EMBL-NM031154; DDBJ-NM031154;
GenBank-NM012584; EMBL-NM012584; DDBJ-NM012584; GenBank-NM031682;
EMBL-NM031682; DDBJ-NM031682; GenBank-NM013083; EMBL-NM013083;
DDBJ-NM013083; GenBank-NM017085; EMBL-NM017085; DDBJ-NM017085;
GenBank-NM012753; EMBL-NM012753; DDBJ-NM012753; GenBank-NM017286;
EMBL-NM017286; DDBJ-NM017286; GenBank-NM019286; EMBL-NM019286;
DDBJ-NM019286
ED Entered STN: 27 Oct 2006
Last Updated on STN: 27 Oct 2006
AB Four triazole fungicides were studied using toxicogenomic techniques to
identify potential mechanisms of action. Adult male Sprague-Dawley rats
were dosed for 14 days by gavage with fluconazole, myclobutanil,
propiconazole, or triadimefon. Following exposure, serum was collected

for hormone measurements, and liver and testes were collected for histology, enzyme biochemistry, or gene expression profiling. Body and testis weights were unaffected, but liver weights were significantly increased by all four triazoles, and hepatocytes exhibited centrilobular hypertrophy. Myclobutanil exposure increased serum testosterone and decreased sperm motility, but no treatment-related testis histopathology was observed. We hypothesized that gene expression profiles would identify potential mechanisms of toxicity and used DNA microarrays and quantitative real-time PCR (qPCR) to generate profiles. Triazole fungicides are designed to inhibit fungal cytochrome P450 (CYP) 51 enzyme but can also modulate the expression and function of mammalian CYP genes and enzymes. Triazoles affected the expression of numerous CYP genes in rat liver and testis, including multiple Cyp2c and Cyp3a isoforms as well as other xenobiotic metabolizing enzyme (XME) and transporter genes. For some genes, such as Ces2 and Udpgtr2, all four triazoles had similar effects on expression, suggesting possible common mechanisms of action. Many of these CYP, XME and transporter genes are regulated by xeno-sensing nuclear receptors, and hierarchical clustering of CAR/PXR-regulated genes demonstrated the similarities of toxicogenomic responses in liver between all four triazoles and in testis between myclobutanil and triadimefon. Triazoles also affected expression of multiple genes involved in steroid hormone metabolism in the two tissues. Thus, gene expression profiles helped identify possible toxicological mechanisms of the triazole fungicides.

L11 ANSWER 15 OF 40 CAPLUS
AN 2005:1223575 CAPLUS
DN 144:65267
TI Gene Expression Patterns in Estrogen (Nonylphenol) and Aryl Hydrocarbon Receptor Agonists (PCB-77) Interaction Using Rainbow Trout (Oncorhynchus Mykiss) Primary Hepatocyte Culture
AU Skjetne Mortensen, Anne; Tolfsen, Christina; Arukwe, Augustine
CS Department of Biology, Norwegian University of Science and Technology

(NTNU), Trondheim, Norway
SO Journal of Toxicology and Environmental Health, Part A (2006), 69(1-2), 1-19
CODEN: JTEHF8; ISSN: 1528-7394
PB Taylor & Francis, Inc.
DT Journal
LA English
AB It was previously reported that in vivo exposure of fish to combined aryl hydrocarbon receptor agonist (AhR; 3,3',4,4'-tetrachlorobiphenyl, PCB-77) and estrogen receptor agonist (ER; nonylphenol, NP) resulted in potentiation and inhibition (depending on dose ratio, sequential order of exposure, and seasonal changes) of NP-induced responses by PCB-77. The expts. described in this report extend this study by testing whether the effects of PCB-77 on NP-induced ER signaling are mediated through AhR-induced transcriptional suppression of target genes. Trout hepatocytes were isolated by a two-step collagenase perfusion method. After 48-h culture, hepatocytes were exposed to 5 or 10 μM nonylphenol (NP) singly and in combination with PCB-77 at 0.1, 1, and 10 μM. Cells were harvested after 96-h exposure and processed for RNA isolation. Gene expression patterns were quantified using real-time polymerase chain reaction (PCR) with specific primer sets and by Northern blot. Exposure of cells to NP caused significant elevation of ERα, ERβ, Vtg, and Zrp mRNA expressions, while combined exposure with PCB-77 concentration inhibited NP-induced ERs and their target gene expressions. Exposure of trout hepatocytes to PCB-77 alone caused a rapid induction of cytochrome P 450 (CYP) 1A1 mRNA, and combined exposure with NP caused significant reduction in PCB-77 induced CYP1A1 gene expression. Exposure of cells to PCB-77 concns. induced significant reduction in AhRα mRNA (except 1 μM PCB-77, which caused the induction of AhRα mRNA levels). AhRβ mRNA levels in the cells were inhibited after 96-h exposure to PCB-77, while combined exposure with 5 μM NP restored the PCB-77-inhibited AhRβ mRNA levels to baseline. Taken together, the

overall results in this study show that PCB-77 suppresses the gene expression of the ERs and their target genes by transcription mechanism(s). The roles of AhRs in mediating these responses seem to involve the ligand-activated AhR transcriptional induction of CYP1A1. In addition to their frequently described functions as activators of metabolic potentiation and detoxification of various foreign chems., data presented in the present study point to other endogenous functions of AhRs that need to be studied further.
RE.CNT 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2005:673383 CAPLUS
DN 143:167619
TI Method for establishing a singular cell model capable of modulating drug biotransformation by altering gene expression of enzymes involved in human
IN Castell Ripoll, Jose Vicente; Jover Atienza, Ramiro; Gomez-Lechon, Maria Jose
PA Advanced In Vitro Cell Technologies, S. L., Spain
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005068611	A1	20050728	WO 2004-EP339	20040119

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2553995 A1 20050728 CA 2004-2553995 20040119
EP 1709158 A1 20061011 EP 2004-703149 20040119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK
JP 2007518411 T 20070712 JP 2006-549878 20040119
US 20050176147 A1 20050811 US 2004-775914 20040210
US 20080044845 A1 20080221 US 2006-597286 20061020
PRAI WO 2004-EP339 W 20040119
AB The invention describes the use of expression vectors coding for the sense
and anti-sense mRNA of the Phase I and Phase II drug biotransformation
enzymes in human cells. Such vectors can modulate the specific expression
of an enzyme without affecting the other enzymes. This singular cell
model can reproduce in vitro the metabolic idiosyncrasy of humans. It is
applicable in the development of new drugs, especially in the study of metabolism,
potential idiosyncratic hepatotoxicity and drug interactions.
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2005:71066 CAPLUS
DN 142:170050
TI DEF domain-containing members of the MAP kinase pathway and their use in
screening for drug inhibitors
IN Blenis, John; Murphy, Leon O.
PA Harvard College, USA
SO PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE
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PI WO 2005007090 A2 20050127 WO 2004-US21514 20040702
WO 2005007090 A3 20090409
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG, AP, EA, EP, OA
PRAI US 2003-484761P P 20030703
AB Mitogen-activated protein (MAP) kinases (e.g., ERK1/2) phosphorylate a
variety of target proteins including, for example, several immediate-early
gene products (e.g., Fos, Myc, and Jun family proteins). Certain
phosphorylation reactions require binding of the MAP kinase to the DEF
domain of the target protein. Inhibitors that block this interaction may
be useful therapeutics for human disease, including as antineoplastic
agents. This invention provides several advantages over known therapies
that directly target the MAP kinase signaling cascade. Typically, most
compds. that inhibit the MAP kinase pathway are non-specific and inhibit
more than one enzyme, and the targeted inhibited kinases are not available
to perform normal physiol. functions necessary for cell survival, whereas
therapeutic methods of the present invention inhibit the activation of
particular target proteins and leave the MAP kinases enzymically active
and available to phosphorylate other non-DEF domain-containing proteins.

Thus, DEF domains are identified in a large number of proteins, and the principles of the invention are exemplified using the immediate-early gene, c-Fos. Screening assays useful for identifying compds. that inhibit the MAP kinase-DEF domain interaction are also disclosed.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L11 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2005:4584 CAPLUS
DN 142:107752
TI Prostaglandin E2 down-regulation of cytochrome P-450 2B1 expression induced by phenobarbital is through EP2 receptor in rat hepatocytes
AU Li, Chien-Chun; Shen, Hui-Lan; Lii, Chong-Kuei; Liu, Kai-Li; Yang, Jaw-Ji; Chen, Haw-Wen
CS Department of Nutritional Science, Chung Shan Medical University, Taichung, Taiwan
SO Biochemical and Biophysical Research Communications (2005), 327(2), 424-430
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
AB Cytochrome P 450 is an important bioactivation-detoxification system in vivo. Its expression is regulated by foreign chems. and dietary factors, and lipids have been found to regulate its gene expression. The authors showed previously that prostaglandin E2 (PGE2), a fatty acid metabolite, down-regulates cytochrome P 450 2B1 (CYP 2B1) expression induced by phenobarbital. The objective of the present study was to determine whether PGE2 type 2 receptor (EP2)-which is coupled to Gs-protein when bound by PGE2, leading to cAMP production-is involved in this down-regulation. The authors also determined the possible roles of EP2 downstream pathways in this down-regulation. The authors used a primary rat hepatocyte culture model in which EP2 was shown to be present to study this question. The intracellular cAMP concentration in primary rat hepatocytes was significantly higher after treatment with 1 μM PGE2 than after treatment with 0,

0.01, or 0.1 μM PGE2. Butaprost, an EP2 agonist, down-regulated CYP 2B1 expression in a dose-dependent manner. SQ22536, an adenylate cyclase inhibitor, reversed the down-regulation by PGE2 as did H-89, a protein kinase A inhibitor. These results suggest that EP2 and the downstream pathways of cAMP and protein kinase A are involved in the down-regulation of CYP 2B1 expression by PGE2 in the presence of phenobarbital.

OSC.G 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2004:636901 CAPLUS

DN 141:200616

TI Sexually dimorphic P450 gene expression in liver-specific hepatocyte nuclear factor 4α-deficient mice

AU Wiwi, Christopher A.; Gupte, Minita; Waxman, David J.

CS Division of Cell and Molecular Biology, Department of Biology, Boston University, Boston, MA, 02215, USA

SO Molecular Endocrinology (2004), 18(8), 1975-1987 CODEN: MOENEN; ISSN: 0888-8809

PB Endocrine Society

DT Journal

LA English

AB Hepatocyte nuclear factor (HNF) 4α is a liver-enriched nuclear receptor that plays a critical role in regulating the expression of numerous hepatic genes, including members of the cytochrome P 450 (CYP) superfamily, several of which are expressed in a sex-dependent manner. Presently, we use a liver-specific Hnf4α-deficient mouse model to investigate the role of HNF4α in regulating liver-enriched transcription factors and sexually dimorphic Cyps in liver in vivo. Real-time PCR anal. of RNA isolated from livers of wild-type and Hnf4α-deficient mice revealed the following: (1) HNF4α exerts both pos. regulation (Hnfα, C/ebpα, and C/ebpβ) and neg. regulation (Hnf3α and the HNF4α coactivator Pgc-1α) on liver transcription factor expression; (2) a strong dependence on HNF4α characterizes several male-predominant Cyps (2d9 and 8b1), female-predominant Cyps (2b10, 2b13, 3a41, and 3a44) and Cyps, whose expression is sex independent (3a11, 3a25); (3) HNF4α confers a unique, pos. regulation of two male-expressed genes (Cyp4a12 and GSTπ)

and a neg. regulation of several female-predominant genes (Cyp2a4, Cyp2b9, Hnf3β, and Hnf6), both of which are manifest in male but not female mouse liver. These trends were confirmed at the protein level by Western blot anal. using antibodies raised to Cyp2a, Cyp2b, and Cyp3a family members. Thus, HNF4α is an essential player in the complex regulatory network of liver-enriched transcription factors and the sexually dimorphic mouse Cyp genes that they regulate. HNF4α is proposed to contribute to the sex specificity of liver gene expression by pos. regulating a subset of male-specific Cyp genes while concomitantly inhibiting the expression of certain female-specific Cyps and liver transcription factors, by mechanisms that are operative in male, but not female, mouse liver.

OSC.G 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (36 CITINGS)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2004:1020353 CAPLUS

DN 142:190313

TI Induction of CYP3A4 by efavirenz in primary human hepatocytes: Comparison with rifampin and phenobarbital

AU Hariparsad, Niresh; Nallani, Srikanth C.; Sane, Rucha S.; Buckley, Donna J.; Buckley, Arthur R.; Desai, Pankaj B.

CS College of Pharmacy, University of Cincinnati Medical Center, Cincinnati, OH, USA

SO Journal of Clinical Pharmacology (2004), 44(11), 1273-1281
CODEN: JCPCBR; ISSN: 0091-2700

PB Sage Publications

DT Journal

LA English

AB The antiretroviral agent efavirenz enhances the systemic clearance of coadministered drugs that are cytochrome P 450 (CYP) 3A4 substrates. The mechanism of the apparent increase in CYP3A4 activity by efavirenz and the magnitude of change relative to other known inducers are not known. The authors tested the hypothesis that increased enzymic activity by efavirenz entails CYP3A4 induction and activation of the human

pregnane X receptor (hPXR), a key transcriptional regulator of CYP3A4.
Employing primary cultures of human hepatocytes, they compared the CYP3A4
inductive effects of efavirenz (1-10 μM) to rifampin (10 μM) and
phenobarbital (2 mM). A cell-based reporter assay was employed to assess
hPXR activation. The authors observed that efavirenz caused a
concentration-dependent CYP3A4 induction and hPXR activiation. Based on the
CYP3A4 activity assay, the average magnitude of induction by efavirenz (5-10
μM) was approx. 3- to 4-fold. In comparison, phenobarbital (2 mM) and
rifampin (10 μM) caused a 5- and 6-fold induction, resp.
OSC.G 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5
AN 2004:379281 CAPLUS
DN 141:48385
TI Role of hepatocyte nuclear factor 3γ in the expression of human CYP2C genes
AU Bort, Roque; Gomez-Lechon, M. Jose; Castell, Jose V.; Jover, Ramiro
CS Centro de Investigacion, Unidad de Hepatologia Experimental, Hospital
Universitario La Fe, Valencia, E-46009, Spain
SO Archives of Biochemistry and Biophysics (2004), 426(1), 63-72
CODEN: ABBIA4; ISSN: 0003-9861
PB Elsevier Science
DT Journal
LA English
AB Hepatocyte nuclear factor 3γ (HNF-3γ) is an important transcription factor for the maintenance of specific liver
functions. However, its relevance in the expression of human cytochrome P
450 (CYP) genes has not yet been explored. Several HNF3
putative binding sites can be identified in human CYP2C 5'-flanking
regions. Gene reporter expts. with proximal promoters revealed that
HNF-3γ transactivated CYP2C8, CYP2C9, and CYP2C19 (25-, 4-, and
4-fold, resp.), but it did not trans-activate CYP2C18. However,
overexpression of HNF-3γ in hepatoma cells by means of a recombinant
adenovirus induced CYP2C9, CYP2C18, and CYP2C19 mRNA (4.5-, 20-,
and 50-fold, resp.) but did not activate endogenous CYP2C8. The lack of

effect of HNF-3γ on endogenous CYP2C8 could be reversed by treating cells with the deacetylase inhibitor, trichostatin A, suggesting the existence of chromatin condensation around functional HNF3 elements in this gene. Thus, HNF3γ is an important transcription factor for the hepatic-specific expression of human CYP2C genes. The results also evidence that efficient transfection tools, such as adenoviral vectors, may be decisive for assessing the role of transcription factor on chromatin organized genes.

OSC.G 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 22 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 6

AN 2003:292629 BIOSIS

DN PREV200300292629

TI Role of the hepatocyte nuclear factor 4alpha in control of the pregnane X receptor during fetal liver development.

AU Kamiya, Akihide; Inoue, Yusuke; Gonzalez, Frank J. [Reprint Author]

CS Laboratory of Metabolism, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Building 37, Room 2A19, Bethesda, MD, 20892, USA
fjgonz@helix.nih.gov

SO Hepatology, (June 2003) Vol. 37, No. 6, pp. 1375-1384. print.
ISSN: 0270-9139 (ISSN print).

DT Article

LA English

ED Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003

AB The fetal liver, the major site of hematopoiesis during embryonic development, acquires additional functions near birth. Among the important liver functions is the response to xenobiotic exposure due to expression of several cytochromes P450 (CYP) and drug efflux transporters. Expression of these genes is regulated by nuclear receptors such as the pregnane X receptor (PXR). In this study, regulation of xenobiotic responses during fetal liver development was analyzed using a fetal hepatocyte primary culture system derived from embryonic

day 15 (E15) livers. Hepatocyte nuclear factor (HNF) 4alpha regulates the expression of many genes preferentially in the liver. Expression of several xenobiotic response genes as well as HNF4alpha was increased in fetal hepatocytes stimulated by the hepatic maturation factors oncostatin M (OSM) and Matrigel. To determine the contribution of HNF4alpha to xenobiotic responses in the fetal liver, fetal hepatocytes containing floxed HNF4alpha alleles were cultured and the HNF4alpha gene was inactivated by infection with an adenovirus containing the Cre gene. Expression of CYP3A11 and PXR was suppressed by inactivation of HNF4alpha. An HNF4alpha binding site was characterized in the PXR promoter and found to be required for activation of the PXR promoter in fetal hepatocytes. In conclusion, HNF4alpha is the key transcription factor regulating responses to xenobiotics through activation of the PXR gene during fetal liver development.

L11 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2003:157294 CAPLUS
DN 139:240059
TI Telomerase reconstitution immortalizes human fetal hepatocytes without disrupting their differentiation potential
AU Wege, Henning; Le, Hai T.; Chui, Michael S.; Liu, Li; Wu, Jian; Giri, Ranjit; Malhi, Harmeet; Sappal, Baljit S.; Kumaran, Vinay; Gupta, Sanjeev; Zern, Mark A.
CS Transplant Research Institute, Davis Medical Center, University of California, Sacramento, CA, USA
SO Gastroenterology (2003), 124(2), 432-444
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB The availability of in vitro expandable human hepatocytes would greatly advance liver-directed cell therapies. Therefore, we examined whether human fetal hepatocytes are amenable to telomerase-mediated immortalization without inducing a transformed phenotype and disrupting their

differentiation potential. Telomerase is a ribonucleoprotein that plays a pivotal role in maintaining telomere length and chromosome stability. Human somatic cells, including hepatocytes, exhibit no telomerase activity. Consequently, their telomeres progressively shorten with each cell cycle until critically short telomeres trigger replicative senescence. The catalytic subunit, telomerase reverse transcriptase, was expressed in human fetal hepatocytes. Transduced cells were characterized for telomerase activity, telomere length, proliferative capacity, hepatocellular functions, oncogenicity, and their in vivo maturation potential. The expression of human telomerase reverse transcriptase restored telomerase activity in human fetal hepatocytes. Telomerase-reconstituted cells were capable of preserving elongated telomeres, propagated in culture beyond replicative senescence for more than 300 cell doublings (to date), and maintained their liver-specific nature, as analyzed by a panel of hepatic growth factors, growth factor receptors, and transcription factors as well as albumin, glucose-6-phosphatase, glycogen synthesis, cytochrome P 450 (CYP) expression profiles, and urea production Moreover, the immortalized cells exhibited no oncogenicity, and no up-regulation of c-Myc was detected. The cells engrafted and survived in the liver of immunodeficient mice with hepatocellular gene expression. Reconstitution of telomerase activity induces indefinite replication in human fetal hepatocytes and offers unique opportunities for examining basic biol. mechanisms and for considering development of stable cell lines for liver-directed therapies.

OSC.G 52 THERE ARE 52 CAPLUS RECORDS THAT CITE THIS RECORD (52 CITINGS)

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 7

AN 2003:625209 CAPLUS

DN 140:12327

TI Human hepatocytes as a tool for studying toxicity and drug metabolism

AU Gomez-Lechon, M. J.; Donato, M. T.; Castell, J. V.; Jover, R.

CS Centro de Investigacion, Hospital La Fe, Valencia, 46009, Spain
SO Current Drug Metabolism (2003), 4(4), 292-312
CODEN: CDMUBU; ISSN: 1389-2002
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Drugs are usually biotransformed into new chemical species that may have either toxic or therapeutic effects. Drug metabolism studies are routinely performed in laboratory animals but, due to metabolic interspecies differences when compared to man, they are not accurate enough to anticipate the metabolic profile of a drug in humans. Human hepatocytes in primary culture provide the closest in vitro model to human liver and the only model that can produce a metabolic profile of a given drug that is very similar to that found in vivo. However their availability is limited due to the restricted access to suitable tissue samples. The scarcity of human liver has led to optimizing the cryopreservation of adult hepatocytes for long-term storage and regular supply. Human hepatocytes in primary culture express typical hepatic functions and express drug metabolizing enzymes. Moreover, qual. and quant. similarities between in vitro and in vivo metabolism of drugs were observed Different strategies have been envisaged to prolong cell survival and delay the spontaneous decay of the differentiated phenotype during culture. Thus, hepatocytes represent the most appropriate model for the evaluation of integrated drug metabolism, toxicity/metabolism correlations, mechanisms of hepatotoxicity, and the interactions (inhibition and induction) of xenobiotics and drug-metabolizing enzymes. However, in view of limitations of primary hepatocytes, efforts are made to develop alternative cellular models (i.e. metabolic competent CYP-engineered cells stably expressing individual CYPs and transient expression of CYPs by transduction of hepatoma cells with recombinant adenoviruses). In summary, several cellular tools are available to address key issues at the earliest stages of drug development for a better candidate selection and hepatotoxicity risk assessment.

L11 ANSWER 25 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN
AN 2004:123379 BIOSIS
DN PREV200400116660
TI Oxygen modulation of cytochrome p450 pathways: Role of oxygen gradients
and HIF-1alpha in hepatocytes in vitro.
AU Allen, Jared W. [Reprint Author]; Johnson, Randall S. [Reprint Author];
Bhatia, Sangeeta N. [Reprint Author]
CS University of California San Diego, La Jolla, CA, USA
SO Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 270A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the
Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American
Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
AB Background: Oxygen is a key modulator of hepatocyte function in
both normal physiology and disease states. In particular,
microenvironmental oxygen levels have been implicated in regeneration,
zonation-dependent phenomena, xenobiotic metabolism and cellular injury.
However, the mechanisms by which cells, and in this case,
hepatocytes sense and respond to a wide range of oxygen tensions
are not fully elucidated. The aim of this study was to investigate
oxygen-dependent changes in expression of several cytochrome p450
isoenzymes (CYP1A1, CYP2B, CYP3A) and the role of hypoxia inducible
factor-1alpha (HIF-1a) in these processes. Methods: Cocultures of rat
hepatocytes and J2-3T3 fibroblast were placed in a biomimetic
parallel-plate perfusion reactor to assess the role of oxygen gradients on
induction of CYP2B and CYP3A by phenobarbitol and dexamethasone,
respectively. Oxygen transport in the bioreactor as a function of flow
rate and inlet oxygen tension was mathematically modeled and compared to
experimental measurements. Viability of bioreactor cultures was
determined using fluorescence microscopy and. CYP2B and CYP3A protein
levels were evaluated by Western blot. To specifically determine the role

hypoxia in CYP1A1 gene expression, transgenic mouse hepatocytes were cultured in a collagen sandwich system. Using Cre-Lox technology, hepatocytes isolated from transgenic mice were treated with adenovirus enabling selective excision of genes encoding HIF-1a, a key hypoxia-responsive transcription factor or von Hippel Lindau (VHL), which is implicated in post-translational HIF-1a degradation under normoxia. Cultures were then subjected to treatment with 3-methylcholanthrene and/or hypoxia. Gene expression of HIF1a target genes PGK and VEGF as well as CYP1A1, a target of the dioxin/AhR pathway were determined using quantitative PCR. Results: Phenotypically stable hepatocyte/fibroblast cocultures remained viable in perfusion culture under an experimentally-validated physiologic gradient from 76 mmHg to 25 mmHg oxygen. CYP2B and CYP3A protein levels were increased in bioreactor cultures, demonstrating the benefit of perfusion and nutrient gradients that mimic the hepatocyte microenvironment in vivo. Regional variations in CYP expression along the length of the reactor were observed and were found to vary as a function of oxygen and hormone availability. To further examine oxygen sensing mechanisms in hepatocytes, we examined the proposed interactions of the hypoxia and dioxin signaling pathways at the level of HIF1a that result in reduced expression of CYP1A1 under hypoxia. Adenoviral-mediated gene excision resulted in greater than 90% deletion of the HIF-1a and VHL. 3MC-mediated CYP1A1 expression was 6-fold higher than untreated cells in HIF1a-null cultures under normoxia but only 1.5-fold higher under hypoxia, indicating that hypoxia repression of CYP1A1 induction is HIF1a-independent. VHL-null cultures, which allow for active HIF-1a targeting under normoxic conditions, also showed no interference with CYP1A1 induction by 3-MC. Conclusions: We have shown that a perfusion culture system that integrates physiologic gradients of oxygen and other soluble stimuli may be preferable to conventional culture systems for studies in which CYP isoenzymes are implicated (drug metabolism,

toxicity, etc). Furthermore, the repression of CYP1A1 expression under hypoxia, which occurs at the level of transcription, is not due to interactions of HIF-1a with the dioxin signaling pathway. High-throughput gene expression analysis of hepatocytes under variable oxygen environments may help identify the factors responsible for hypoxic CYP1A1 repression.

L11 ANSWER 26 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2004:123202 BIOSIS
DN PREV200400116526
TI Hepatic insulin signaling is inhibited by CYP2E1-overexpression.
AU Schattenberg, Jorn M. [Reprint Author]; Wang, Yongjun [Reprint Author]; Rigoli, Raina M. [Reprint Author]; Czaja, Mark J. [Reprint Author]
CS Albert Einstein College of Medicine, Bronx, NY, USA
SO Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 192A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
AB The mechanisms leading to hepatic steatosis and the progression to non-alcoholic steatohepatitis (NASH) are unknown. The development of NASH occurs in association with both cytochrome P450 2E1 (CYP2E1) overexpression, and metabolic abnormalities that include insulin resistance. The high prevalence of insulin resistance in NASH suggests that hepatic steatosis or NASH may result from, and/or contribute to insulin resistance. Insulin resistance is manifested by impaired activation of insulin receptor substrate 1 (IRS-1), a central regulator of downstream effectors of insulin signaling. IRS-1 activation results from tyrosine phosphorylation, but is inhibited by serine phosphorylation. We

hypothesized that oxidative stress caused by CYP2E1 overexpression alters IRS-1 signaling, further contributing to hepatic insulin resistance in NASH. In vitro studies were performed in the non-transformed rat hepatocyte cell line RALA255-10G stably transfected with a CYP2E1 expression vector (S-CYP cells), or empty vector (VEC cells) as a control. S-CYP cells had a 2.5-fold increase in levels of total IRS-1 by Western blot as compared to VEC cells. However, relative tyrosine phosphorylation of IRS-1 following insulin treatment was decreased 40% in S-CYP cells as compared to VEC cells. S-CYP cells had a greater than 6-fold increase in inhibitory IRS-1 serine phosphorylation constitutively and following insulin stimulation. Sustained insulin exposure leads to desensitization by phosphoinositide 3-kinase (PI3K)-dependent IRS-1 degradation. Prolonged insulin treatment induced equivalent IRS-1 degradation in S-CYP and VEC cells, although this process was PI3K-independent in S-CYP cells. Thus, decreased IRS-1 activation in S-CYP cells was not compensated for by a prolongation of IRS-1 signaling. To evaluate the functional significance of decreased IRS-1 signaling in S-CYP cells, activation levels of the IRS-1 regulated protein kinase Akt, glycogen synthase kinase 3 (GSK3) and the forkhead transcription factors Foxo 1 and 3 were examined. Levels of Akt phosphorylation and activity, as determined by in vitro kinase assay, were markedly decreased in S-CYP cells relative to VEC cells constitutively and following insulin stimulation. Insulin-activated Akt phosphorylates and inactivates GSK3 leading to glycogen synthesis. In response to insulin treatment, S-CYP cells had decreased GSK3 phosphorylation compared to VEC cells. Insulin induces Akt-dependent Foxo 1 and 3 phosphorylation resulting in their transcriptional inactivation and down-regulation of the key gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK). In parallel with their reduced Akt activation, S-CYP cells had decreased constitutive and insulin-stimulated phosphorylation of Foxo 1 and 3. This decreased Foxo 1 and 3 inactivation

resulted in a 4-fold increase in steady-state PEPCK mRNA levels in S-
CYP cells when compared to VEC cells. Finally, to examine whether
hepatic IRS-1 signaling was affected in NASH, levels of IRS-1 serine
phosphorylation were determined in mice fed a control, or
methionine-choline deficient (MCD) diet. MCD diet-fed mice developed
steatohepatitis associated with a greater than 3-fold increase in their
levels of inhibitory IRS-1 serine phosphorylation relative to control-fed
mice. Thus, CYP2E1 overexpression in hepatocytes induces increased
inhibitory IRS-1 serine phosphorylation causing decreased IRS-1 signaling
and downstream Akt activation. This failure to activate Akt leads to
decreased GSK inactivation, decreased Foxo 1 and 3 phosphorylation, and
increased PEPCK gene expression, promoting decreased glycogen synthesis
and increased glyconeogenesis. Increased inhibitory IRS-1 serine
phosphorylation also occurs in the MCD diet-induced animal model of NASH.
Down-regulation of insulin signaling through CYP2E1-induced oxidative
stress may therefore promote hepatic insulin resistance in NASH and
further alter glucose homeostasis.

L11 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2002:877338 CAPLUS
DN 137:368258
TI Down-regulation of human CYP3A4 by the inflammatory signal interleukin 6:
molecular mechanism and transcription factors involved
AU Jover, Ramiro; Bort, Roque; Gomez-Lechon, Ma. Jose; Castell, Jose V.
CS Unidad de Hepatologia Experimental, Centro de Investigacion, Hospital
Universitario La Fe, Valencia, 46009, Spain
SO FASEB Journal (2002), 16(13), 1799-1801, 10.1096/fj.02-0195fje
CODEN: FAJOEC; ISSN: 0892-6638
PB Federation of American Societies for Experimental Biology
DT Journal
LA English
AB The hepatic drug-metabolizing cytochrome P 450 (CYP) enzymes are
down-regulated during inflammation. In vitro studies with
hepatocytes have shown that the cytokines released during
inflammatory responses are largely responsible for this CYP

repression. However, the signaling pathways and the cytokine-activated factors involved remain to be properly identified. The authors' research has focused on the neg. regulation of CYP3A4 (the major drug-metabolizing human CYP) by interleukin 6 (IL-6) (the principal regulator of the hepatic acute-phase response). CYP3A4 down-regulation by IL-6 requires activation of the glycoprotein receptor gp130; however, it does not proceed through the JAK/STAT pathway, as demonstrated by the overexpression of a dominant-neg. STAT3 factor by an adenoviral vector. The involvement of IL-6-activated kinases such as extracellular signal-regulated kinase ERK1/2 or p38 is also unlikely, as evidenced by the use of specific chemical inhibitors. It is noteworthy that IL-6 caused a moderated induction in the mRNA of the transcription factor C/EBPβ (CCAAT-enhancer binding protein β) and a marked increase in the translation of C/EBPβ-LIP, a 20-kDa C/EBPPβ isoform lacking a transactivation domain. Adenovirus-mediated expression of C/EBPPβ-LIP caused a dose-dependent repression of CYP3A4 mRNA, whereas overexpression C/EBPα and C/EBPβ-LAP (35 kDa) caused a significant induction. The authors' results support the idea that IL-6 down-regulates CYP3A4 through translational induction of C/EBPβ-LIP, which competes with and antagonizes constitutive C/EBP transactivators. From a clin. point of view, these findings could be relevant in the development of therapeutic cytokines with a less repressive effect on hepatic drug-metabolizing enzymes.

OSC.G 60 THERE ARE 60 CAPLUS RECORDS THAT CITE THIS RECORD (60 CITINGS)

RE.CNT 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 28 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2002:844882 CAPLUS

DN 138:182252

TI Divergence in mechanism between AHR agonists and antagonists in the AHR signal transduction pathway

AU Chen, Guosheng; Chen, Jin Jun; Bunce, Nigel J.

CS Department of Chemistry and Biochemistry, University of Guelph, Guelph, ON, N1G 2W1, Can.

SO Organohalogen Compounds (2002), 55(Dioxin 2002), 445-448
CODEN: ORCOEP; ISSN: 1026-4892
PB Spanish Council for Scientific Research, Laboratory of Dioxins
DT Journal
LA English
AB The mechanism of antagonism on each step of the Ah receptor signal transduction pathway leading to the induction of cytochrome P 450 1A1 in primary rat hepatocytes was studied. The point of divergence in the mechanism of action between the potent and nonpotent ligands was also identified. The interaction of PBDE congeners and TCDD on each step of the Ah receptor signaling system was also discussed. TCDD binds with high affinity to the Ah receptor; the affinity of other ligands is generally determined by competition with [3H]TCDD using the HAP assay. Less potent ligands totally displace TCDD at sufficiently high concentration Ligand binding is initially reversible, but the AhR-HAH complex is then transformed to a form that has an increased binding affinity for the bound ligand. PBDE congeners 77, 126, and 119 showed increasing CYP1A1 protein monotonically with dose and the maximum induced levels were similar to the reference of 10-9M TCDD. The strong induction of CYP 1A1 protein was consistent with their greater AhR activation to the DRE binding form by these congeners. Congeners 66, 100, 153, and 183 were moderate CYP 1A1 inducers; induction only occurred at high concentration
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 29 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 8
AN 2002:563105 BIOSIS
DN PREV200200563105
TI Transduction of immortalized human hepatocytes with p21 to enhance differentiated phenotypes.
AU Kunieda, Takemi; Kobayashi, Naoya [Reprint author]; Sakaguchi, Masakiyo; Okitsu, Teru; Totsugawa, Toshinori; Watanabe, Takamasa; Matsumura,

Toshihisa; Maruyama, Masanobu; Noguchi, Hirofumi; Takesue, Michihiko;
Shibata, Norikuni; Ohmoto, Kenji; Fujiwara, Toshiyoshi; Yamamoto, Shinichiro; Tanaka, Noriaki

CS Department of Surgery, Okayama University Graduate School of Medicine and
Dentistry, 2-5-1 Shikata-cho, Okayama, 700-8558, Japan
immortal@md.okayama-u.ac.jp

SO Cell Transplantation, (2002) Vol. 11, No. 5, pp. 421-428. print.
ISSN: 0963-6897.
DT Article
LA English
ED Entered STN: 30 Oct 2002
Last Updated on STN: 30 Oct 2002

AB We previously constructed an immortal human hepatocyte line NKNT-3 with a simian virus 40 T antigen (SV40T) to develop cell-based biological therapies. p21 is a molecule that regulates the transition from the G1 phase to the S phase of the cell cycle. Investigators have demonstrated that overexpression of p21 induces differentiation in various cell lines. In the current study we examined the effect of p21 on differentiated phenotypes of SV40T-immortalized NKNT-3 cells. A replication-deficient adenovirus vector expressing a human wild-type p21 cDNA under the control of the CMV promoter (Ad5CMVp21) and a human wild-type p21 protein fused to the protein transduction domain from the human immunodeficiency virus (HIV) TAT protein (TAT/p21) were utilized to achieve efficient delivery of p21 into NKNT-3 cells. Morphological alterations, cell cycle progression, and expression of albumin and p-450 associated enzymes (CYPs) 3A4 and 2C9 were evaluated in NKNT-3 cells treated with Ad5CMVp21 and TAT/p21. Efficient adenovirus-based p21 transfer and TAT-mediated p21 protein delivery were confirmed in NKNT-3 cells in an immunofluorescence study and Western blotting analysis. Transduction of NKNT-3 cells with p21 predominantly arrested the cell cycle at the G1 checkpoint, resulting in differentiated hepatic phenotypes in morphology and improvement in protein expression of albumin, CYP 3A4, and CYP C29. We here show that exogenous expression of p21 augments cellular differentiation in immortalized human

NKNT-3 cells.

L11 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 9
AN 2002:706086 CAPLUS
DN 138:84120
TI Improvement in the differentiated hepatic phenotype of immortalized human
hepatocytes by adenovirus mediated p21 gene transfer
AU Kobayashi, Naoya; Sakaguchi, Masakiyo; Okitsu, Teru; Totsugawa, Toshinori;
Maruyama, Masanobu; Matsumura, Toshihisa; Watanabe, Takamasa; Noguchi,
Hirofumi; Kosaka, Yoshikazu; Fujiwara, Toshiyoshi; Tanaka, Noriaki
CS Department of Surgery, Okayama University Graduate School of Medicine and
Dentistry, Okayama, 700-8558, Japan
SO ASAIO Journal (2002), 48(4), 355-359
CODEN: AJOUET; ISSN: 1058-2916
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The p21 mol., a potent cyclin dependent kinase inhibitor, regulates the
transition from the G1 phase to the S phase of the cell cycle and is
involved in terminal cellular differentiation. The overexpression of p21
has been shown to induce differentiation in various cell lines. We have
made an effort to establish a reliable human hepatocyte cell
line as a source of hepatic function in bioartificial liver (BAL) therapy.
In this work, we investigated the effect of p21 on the differential
phenotype of simian virus 40 large T antigen (SV40Tag) immortalized human
hepatocytic NKNT-3 cells. A recombinant adenoviral
vector expressing a p21 gene under control of the cytomegalovirus (CMV)
promoter (Ad-p21) was used to efficiently transfer genes into NKNT-3
cells. The morphol. alterations, the cell cycle progression, and the
expression of P 450 associated enzymes (CYPs) were carefully examined in NKNT-3
cells that had been infected with Ad-p21. Adenovirus mediated
gene delivery of p21 was efficiently achieved in NKNT-3 cells without
affecting cellular structure. After Ad-p21 infection, NKNT-3 cells were
G0/G1 arrested in cell cycle anal. NKNT-3 cells that had been infected

with Ad-p21 showed differentiated hepatic phenotypes in morphol. and improvement in protein expression of CYP 3A4 and CYP 2C9. In the present work, we demonstrate that the exogenous expression of p21 enhances the differential phenotype of immortalized hepatocytic NKNT-3 cells.
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 31 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 10
AN 2002:611337 BIOSIS
DN PREV200200611337
TI Metabolism of heterocyclic aromatic amines by human hepatocytes and cytochrome P4501A2.
AU Turesky, Robert J. [Reprint author]; Guengerich, F. Peter; Guillouzo, Andre; Langouet, Sophie
CS National Center for Toxicological Research, 3900 NCTR Dr., HFT 100, Jefferson, AR, 72079-9502, USA
rturesky@nctr.fda.gov; sophie.langouet@rennes.inserm.fr
SO Mutation Research, (30 September, 2002) No. 506-507, pp. 187-195. print.
CODEN: MUREAV. ISSN: 0027-5107.
DT Article
LA English
ED Entered STN: 27 Nov 2002
Last Updated on STN: 27 Nov 2002
AB The metabolism of 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo (4,5-b)pyridine (PhIP) was investigated in primary human and rat hepatocytes. The genotoxic metabolites 2-(hydroxyamino)-3,8-dimethylimidazo(4,5-f)quinoxaline (HONH-MeIOx) and 2-(hydroxyamino)-1-methyl-6-phenylimidazo(4,5-b)pyridine (HONH-PhIP), which are formed by cytochrome P4501A2 (CYP1A2), were detected as stable N2-glucuronide and N2- and N3-glucuronide conjugates, respectively. These products accounted for as much as 10% of the amount of MeIQx and 60% of PhIP added to human hepatocytes. Significantly lower amounts of these products were formed in rat hepatocytes. The phase II conjugates N2-(3,8-dimethylimidazo(4,5-f)quinoxalin-2-yl-sulfamic acid

(MeIQx-N2-SO3H) and N2-(beta-1-glucosiduronyl)-2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx-N2-Gl), as well as the 7-oxo derivatives of MeIQx and N-desmethyl-MeIQx, 2-amino-3,8-dimethyl-6-hydro-7H-imidazo(4,5-f)quinoxalin-7-one (7-oxo-MeIQx), and 2-amino-6-hydro-8-methyl-7H-imidazo(4,5-f)quinoxalin-7-one (N-desmethyl-7-oxo-MeIQx) were also identified. A novel CYP1A2-derived metabolite was characterized as 2-amino-3-methylimidazo(4,5-f)quinoxaline-8-carboxylic acid (IQx-8-COOH) and was the predominant metabolite formed in human hepatocytes exposed to MeIQx at levels approaching human exposure. Unlike human hepatocytes, rat cell preparations, even following pretreatment with the potent CYP1A1/CYP1A2 inducer 3-methylcholanthrene (3-MC) did not produce IQx-8-COOH but did catalyze the formation of 2-amino-3,8-dimethyl-5-hydroxyimidazo(4,5-f)quinoxaline (5-HO-MeIQx) as a major CYP-mediated detoxication product. In the case of PhIP, direct glucuronidation of the N2 and N3 positions also occurred in human and rat hepatocytes. Glucuronide and sulfate conjugates of 2-amino-4'-hydroxy-1-methyl-6-phenylimidazo(4,5-b)pyridine (4'-HO-PhIP) were detected as relatively minor metabolites in human hepatocytes but were the major products formed in rat hepatocytes, accounting for up to 50% of the metabolism. Rat CYP1A2, but not the human ortholog, significantly contributes to 4'-hydroxylation of PhIP. Important differences exist between human and rat liver enzymes in catalytic activity and regioselectivity of MeIQx and PhIP metabolism. Some human hepatocyte preparations are more active at transforming MeIQx and PhIP to a genotoxic species than rat hepatocytes pretreated with potent inducer 3-MC. These pronounced interspecies differences in metabolism of MeIQx and PhIP may affect the biological activity of these mutagens and must be considered when assessing human health risk.

L11 ANSWER 32 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 11

AN 2001:174237 BIOSIS

DN PREV200100174237

TI cAMP mediated upregulation of CYP2A5 in mouse hepatocytes.

AU Viitala, Pirkko; Posti, Katja; Lindfors, Aija; Pelkonen, Olavi; Raunio,

Hannu [Reprint author]
CS Department of Pharmacology and Toxicology, University of Kuopio, FIN-70211, Kuopio, Finland
SO Biochemical and Biophysical Research Communications, (January 26, 2001)
Vol. 280, No. 3, pp. 761-767. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 11 Apr 2001
Last Updated on STN: 18 Feb 2002
AB CYP2A5 is induced by a large number of chemicals including some cAMP modifiers. In a primary hepatocyte model, stimulation of the cAMP signal transduction pathway by glucagon and isoproterenol, acting via specific G-protein coupled plasma membrane receptors, produced up to 17-fold increases in the marker activity of CYP2A5, coumarin 7-hydroxylase. In contrast, glucagon and isoproterenol caused no significant effects on two other major CYP forms, CYP2B10 and CYP1A1/2. Phenobarbital (PB) elicited a 3-fold increase in CYP2A5 expression (catalytic activity and mRNA), while the cAMP and protein kinase A (PKA) stimulators dibutyryl-cAMP, forskolin and Sp-cAMPs caused up to 18-fold increases in the amount of CYP2A5 mRNA. Coadministration of PB and cAMP/PKA stimulating agents produced an additive inducing effect. The expression of CYP2A5, but not CYP2B10 or CYP1A1/2, in DBA/2 mice displayed a marked circadian rhythm, the level of expression being highest in the evening. These results suggest that among xenobiotic metabolizing CYP enzymes, CYP2A5 is uniquely upregulated by cAMP, possibly having the physiological function of priming the olfactory and digestive systems for nocturnal feeding.

L11 ANSWER 33 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 12
AN 2001:151846 BIOSIS
DN PREV200100151846
TI Cytochrome P450 regulation by hepatocyte nuclear factor 4 in human hepatocytes: A study using adenovirus-mediated antisense targeting.
AU Jover, Ramiro; Bort, Roque; Gomez-Lechon, Maria J.; Castell, Jose V.

[Reprint author]
CS Unidad de Hepatologia Experimental, Centro de Investigacion, Hospital
Universitario La Fe, SVS, Avda. Campanar 21, E-46009, Valencia, Spain
Jose.Castell@uv.es
SO Hepatology, (March, 2001) Vol. 33, No. 3, pp. 668-675. print.
CODEN: HPTLD9. ISSN: 0270-9139.
DT Article
LA English
ED Entered STN: 28 Mar 2001
Last Updated on STN: 15 Feb 2002
AB Hepatocyte nuclear factor 4 (HNF4) is a member of the nuclear receptor super-family that has shown activating effects on particular cytochrome P450 (CYP) promoters from several species. However, its role in the regulation of human CYPs in the liver is still poorly understood, as no comprehensive studies in human-relevant models have been performed. In the present study, we have investigated whether HNF4 plays a general role in the expression of 7 major CYP genes in primary cultured human hepatocytes. To this end, we developed an adenoviral vector for efficient expression of HNF4 antisense RNA. Transduction of human hepatocytes with the recombinant adenovirus resulted in a time-dependent increase in the antisense transcript, followed by a concomitant decrease in apolipoprotein C III mRNA (a target gene of HNF4). Specificity was confirmed by showing that increasing levels of HNF4 antisense RNA resulted in the reduction of HNF4 protein, whereas retinoic X receptor-alpha (RXRalpha), the closest homologous member of the nuclear receptor super-family, was unaffected. Analysis of CYP gene expression in human hepatocytes transfected with HNF4 antisense RNA revealed singular behaviors: (1) CYP3A4, CYP3A5, and CYP2A6 showed an important, dose-dependent down-regulation on blockage of HNF4 translation; (2) a moderate inhibition of CYP2B6, CYP2C9, and CYP2D6 expression was observed (40%-45% reduction); (3) the levels of CYP2E1 were not affected even in the absence of this transcription factor. In conclusion, using an original strategy (efficient antisense RNA expression vector), our study shows that HNF4 is a general regulator supporting the expression of major drug-metabolizing

CYPs in human hepatocytes.

L11 ANSWER 34 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN DUPLICATE 13
AN 2001:433893 BIOSIS
DN PREV200100433893
TI Establishment of a human hepatocyte line (OUMS-29) having CYP 1A1 and 1A2 activities from fetal liver tissue by transfection of SV40 LT.
AU Fukaya, Ken-Ichi; Asahi, Satoru; Nagamori, Seishi; Sakaguchi, Masakiyo;
Gao, Chong; Miyazaki, Masahiro; Namba, Masayoshi [Reprint author]
CS Department of Cell Biology, Institute of Cellular and Molecular Biology,
Okayama University Medical School, Okayama, 700-8558, Japan
mnamba@med.okayama-u.ac.jp
SO In Vitro Cellular and Developmental Biology Animal, (May, 2001) Vol. 37,
No. 5, pp. 266-269. print.
ISSN: 1071-2690.
DT Article
LA English
ED Entered STN: 12 Sep 2001
Last Updated on STN: 22 Feb 2002
AB Immortalized human hepatocytes that can retain functions of drug-metabolizing enzymes would be useful for medical and pharmacological
studies and for constructing an artificial liver. The aim of this study
was to establish immortalized human hepatocyte lines having differentiated
liver-specific functions. pSVneo deoxyribonucleic acid, which contains
large and small T genes in the early region of simian virus 40, was
introduced into hepatocytes that had been obtained from the liver of a
21-wk-old fetus. Neomycin-resistant immortalized colonies were cloned and
expanded to mass cultures to examine hepatic functions. Cells were
cultured in a chemically defined serum-free medium, ASF104, which contains
no peptides other than recombinant human transferrin and insulin. As a
result, an immortal human hepatocyte cell line (OUMS-29) having
liver-specific functions was established from one of the 13 clones.
Expression of CYP 1A1 and 1A2 messenger ribonucleic acid by the
cells was induced by treatment with benz(a)pyrene, 3-methylcholanthrene,

and benz(a)anthracene. OUMS-29 cells had both the polycyclic aromatic hydrocarbon receptor (AhR) and AhR nuclear translocator. Consequently, 7-ethoxyresorufin deethylase activity of the cells was induced time- and dose-dependently by these polycyclic aromatic hydrocarbons. This cell line is expected to be instrumental as an alternative method in animal experiments for studying hepatocarcinogenesis, drug metabolisms of liver cells, and hepatic toxicology.

L11 ANSWER 35 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 14

AN 2000:388023 BIOSIS
DN PREV200000388023
TI Baculovirus vectors repress phenobarbital-mediated gene induction and stimulate cytokine expression in primary cultures of rat hepatocytes.
AU Beck, N. B.; Sidhu, J. S.; Omiecinski, C. J. [Reprint author]
CS Department of Environmental Health, University of Washington, 4225 Roosevelt Way, NE, No. 100, Seattle, WA, 98105-6099, USA
SO Gene Therapy, (August, 2000) Vol. 7, No. 15, pp. 1274-1283. print.
ISSN: 0969-7128.
DT Article
LA English
ED Entered STN: 13 Sep 2000
Last Updated on STN: 8 Jan 2002
AB Baculovirus transfection strategies have proven successful at transferring foreign DNA into hepatoma cells and primary hepatocytes. When testing the utility of these methodologies in cultured hepatocytes, we discovered that the presence of baculovirus disrupts the phenobarbital (PB) gene induction process, a potent transcriptional activation event characteristic of highly differentiated hepatocytes, and repressed expression of the albumin gene. In concert with previous reports from our laboratory demonstrating that increased cAMP levels can completely repress the induction of specific cytochrome P450 (CYP) genes, cAMP concentrations and PKA activities were measured in the primary hepatocytes subsequent to baculovirus exposure. However, neither parameter was affected by the

presence of the virus. To evaluate whether immune response modulation was triggered by baculovirus exposure, RNase protection assays were performed and demonstrated that baculovirus infection activates TNF-alpha, IL-1alpha and IL-1beta expression in the primary hepatocyte cultures. Immunocytochemical experiments indicated that the production of cytokines was likely due to the presence of small numbers of Kupffer cells present in the culture populations. Exogenously added TNF-alpha was also effective in repressing PB induction, consistent with other reports indicating that inflammatory cytokines are capable of suppressing expression of biotransformation enzyme systems. Comparative studies demonstrated the specificity of these effects since exposures of hepatocytes to adenoviral vectors did not result in down-regulation of hepatic gene responsiveness. These results indicate that baculovirus vectors enhance the expression of inflammatory cytokines in primary hepatocyte cultures, raising concerns as to whether these properties will compromise the use of baculovirus vectors for study of cytochrome P450 gene regulation, as well as for liver-directed gene therapy in humans.

L11 ANSWER 36 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 15

AN 2001:46818 BIOSIS

DN PREV200100046818

TI In vitro toxicology in hepatocyte bioreactors-extracellular acidification rate (EAR) in a target cell line indicates hepato-activated transformation of substrates.

AU Koebe, H. G. [Reprint author]; Deglmann, C. J.; Metzger, R.; Hoerrlein, S.; Schildberg, F. W.

CS Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-University, D-81366, Munich, Germany koebe@gch.med.uni-muenchen.de

SO Toxicology, (November 23, 2000) Vol. 154, No. 1-3, pp. 31-44. print. CODEN: TXCYAC. ISSN: 0300-483X.

DT Article

LA English

ED Entered STN: 17 Jan 2001 Last Updated on STN: 12 Feb 2002

AB In this article we introduce an in vitro model for hepato-mediated toxicity testing consisting of a Hepatocyte-Bioreactor connected to a microphysiometer system for monitoring of the extracellular acidification rate (EAR) of cells. The EAR in this system represented the metabolic activity of a tested cell line under the influence of bioreactor supernatant. Cyclophosphamide (CYCL), a well-known hepato-activated cytostatic drug was used as a model substrate because of its widespread clinical use. The predrug CYCL needed CYP 450 dependent activation to its active cytotoxic metabolite 4-OH cyclophosphamide.
Primary pig hepatocytes from slaughterhouse organs were cultured in a collagen sandwich configuration in specially designed flasks and after 3 days introduced into a 50 ml recirculating perfusion system including 30 mug/ml CYCL. In parallel open circuit, this bioreactor was connected to three perfusion chambers of a microphysiometer system housing 1.5 X 105 ZR 751 cells (breast tumor cell line). Bioreactor supernatant including CYCL was pumped at 150 mul/min into the microphysiometer. The recorded EARs under CYCL influence were correlated to controls, which were set to be 100%. After 1 and 7 h of bioreactor supernatant perfusion, including activated CYCL, the ZR 751 cell line showed an EAR of 98.99% +- 3.15 (mean +- SD) and 81.32% +- 10.18 ($P < 0.05$), respectively, as compared to controls (bioreactor supernatant from the identical set-up without CYCL).
The inactivated predrug CYCL showed no effect on the EAR: Perfusion of medium with 30 mug/ml CYCL alone, excluding the bioreactor activation, resulted in an EAR of 100. 11% +- 4.74 (mean +- SD) after 7 h. Thus the presented model of hepato-activated toxicity showed an EAR decrease in the ZR 751 cell line that reflected the toxic activation of the predrug by the bioreactor.

L11 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1997:530513 CAPLUS
DN 127:229161
OREF 127:44519a,44522a
TI An okadaic acid-sensitive pathway involved in the phenobarbital-mediated induction of CYP2B gene expression in primary rat hepatocyte cultures
AU Sidhu, Jaspreet S.; Omiecinski, Curtis J.
CS Department of Environmental Health, University of Washington, Seattle, WA, USA
SO Journal of Pharmacology and Experimental Therapeutics (1997), 282(2), 1122-1129
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB We have previously demonstrated that specific activation of a cAMP-dependent protein kinase A (PKA) pathway resulted in complete repression of phenobarbital (PB)-inducible CYP gene expression in primary rat hepatocyte cultures. In the current investigation, we examined the role of protein phosphatase pathways as potential co-regulators of this repressive response. Primary rat hepatocytes were treated with increasing concns. (0.1-25 nM) of okadaic acid, a potent inhibitor of serine/threonine-specific protein phosphatases PP1 and PP2A. PB induction responses were assessed by use of specific hybridization probes to CYP2B1 and CYP2B2 mRNAs. Okadaic acid completely inhibited the PB induction process in a concentration-dependent manner (IC50, .apprx.1.5-2 nM). Similar repression was obtained with low concns. of other highly specific phosphatase inhibitors, tautomycin and calyculin A. In contrast, exposure of hepatocytes to 1-nor-okadaone or okadaol, neg. analogs of okadaic acid largely devoid of phosphatase inhibitory activity, was without effect on the PB induction process. At similar concns., okadaic acid produced only comparatively weak modulation of the β-naphthoflavone-inducible CYP1A1 gene expression pathway. In addnl. expts., hepatocytes were treated with suboptimal concns. of PKA activators together with

phosphatase inhibitors. Okadaic acid markedly potentiated the repressive effects of dibutyrl-cAMP on the PB induction process. Together, these results indicate that both PKA and protein phosphatase (PP1 and/or PP2A) pathways exert potent and complementary control of the intracellular processes modulating the signaling of PB in cultured primary rat hepatocytes.
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L11 ANSWER 38 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 16
AN 1995:495654 BIOSIS
DN PREV199598519204
TI Induction of cytochrome P-4502B1-related mouse cytochrome P-450 and regulation of its expression by epidermal growth factor/ transforming growth factor alpha in primary hepatocyte culture.
AU Aubrecht, Jiri; Hirsch-Ernst, Karen I. [Reprint author]; Becker-Rabbenstein, Volker; Kahl, Georg Friedrich; Taniguchi, Hisaaki; Hoehne, Martin W.
CS Inst. Pharmacol. Toxicol., Univ. Goettingen, Robert-Koch-Strasse 40, D-37075 Goettingen, Germany
SO Biochemical Pharmacology, (1995) Vol. 50, No. 6, pp. 781-785. CODEN: BCPCA6. ISSN: 0006-2952.
DT Article
LA English
ED Entered STN: 29 Nov 1995
Last Updated on STN: 27 Jan 1996
AB Phenobarbital-dependent induction of mouse cytochrome P-450 (Cyp) orthologous to rat CYP2B1 and its modulation by hepatotrophic growth factors were examined in primary hepatocyte cultures. Compared to rat hepatocytes, induction in mouse hepatocytes was more rapid and effective. Ligands of the EGF receptor, epidermal growth factor, and transforming growth factor a inhibited induction on the basis of protein expression and CYP2B-associated 7-pentoxyresorufin-O-depentylase activity. Furthermore, EGF led to repression of accumulation of corresponding mRNA under phenobarbital, an effect not blocked by inhibition of protein synthesis

under cycloheximide. Ligands of the EGF receptor may contribute towards
the decrease in hepatic CYP expression observed during
(pre)neoplastic development and regeneration.

L11 ANSWER 39 OF 40 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on
STN DUPLICATE 17
AN 1995:483167 BIOSIS
DN PREV199598497467
TI Transforming growth factor-beta-1 down-regulates basal and polycyclic
aromatic hydrocarbon-induced cytochromes P-450 1A1 and 1A2 in adult human
hepatocytes in primary culture.
AU Abdel-Razzak, Ziad; Corcos, Laurent [Reprint author]; Fautrel, Alain;
Campion, Jean-Pierre; Guillouzo, Andre
CS INSERM U 49, Hopital Pontchaillou, 35033 Rennes Cedex, France
SO Molecular Pharmacology, (1994) Vol. 46, No. 6, pp. 1100-1110.
CODEN: MOPMA3. ISSN: 0026-895X.
DT Article
LA English
ED Entered STN: 9 Nov 1995
Last Updated on STN: 14 Dec 1995
AB The effects of interleukin (IL)-1-beta, IL-4, IL-6, tumor necrosis factor
(TNF)-alpha, interferon (IFN)-alpha, IFN-gamma, and transforming
growth factor (TGF)-beta-1 on cytochrome P-450 (CYP)1A
expression and polycyclic aromatic hydrocarbon (PAH)-mediated induction in
primary human hepatocyte cultures were determined. Most
cytokines that were previously found to decrease basal CYP
expression could counteract PAH induction of CYP1A mRNA and its associated
ethoxyresorufin-O-deethylation (EROD) activity. IL-1-beta and TNF-alpha
blocked 3-methylcholanthrene (3-MC)-induced EROD activity by up to 25 and
44%, respectively. IFN-alpha and IFN-gamma antagonized EROD induction by
up to 61 and 70%, respectively. TGF-beta-1 proved to be the most
effective cytokine, because 72 hr of treatment with 2 ng/ml TGF-beta-1
produced nearly 100% inhibition of 3-MC- and benzo(a)pyrene-induced CYPA1
and CYPA2 mRNAs and EROD activity. Treatment with cycloheximide in
combination with 3-MC led to superinduction of CYP1A MRNA, under which
conditions TGF-beta-1 did not block induction, suggesting the requirement

for protein synthesis for the suppressive effect of the cytokine. In addition, TGF-beta-1 augmented AP-1 binding activity, suggesting that fos and/or jun protooncogene products could be implicated in the response. Our results demonstrate that IL-1-beta, TNF-alpha, and IFNs antagonized PAH-mediated induction of CYP1A gene expression in human hepatocytes. In addition, we report the finding of a novel effect of TGF-beta-1, which was able to prevent CYP1A1 and -1A2 induction by two different PAHs.

L11 ANSWER 40 OF 40 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1995:246454 CAPLUS
DN 122:47378
OREF 122:8957a,8960a
TI Effects of epidermal growth factor and transforming growth factor-α on cytochrome P-450 expression in primary culture of mouse hepatocytes
AU Lee, Sang Seop; Lee, Hee Jeong; Jeong, Hye Gwang; Yang, Kyu Hwan
CS Department Life Science, Korea Advanced Institute Science Technology, Taejon, 305-701, S. Korea
SO Environmental Mutagens and Carcinogens (1994), 14(2), 161-9
CODEN: EMCAE8; ISSN: 1012-9634
PB Korean Environmental Mutagen Society
DT Journal
LA Korean
AB Two ligands of EGF receptor, EGF and transforming growth factor-α (TGF-α), were tested for their ability to suppress cytochrome P 450 dependent mixed function oxidase (MFO) system in mouse primary hepatocyte cultures. EGF or TGF-α markedly suppressed induction of ethoxyresorufin-O-deethylase and pentoxyresorufin-O-dealkylase by 2,3,7,8-tetrachlorodibenzo-p-dioxin and phenobarbital, resp. Immunoblot and RNA slot blot anal. revealed that the reduction of MFO by these growth factors was due to the decreased synthesis of corresponding apoproteins and mRNAs. These results suggested that EGF and TGF-α may act on an event(s) required for CYP gene transcription. Pertussis toxin (PT), the G protein modulating agent, when added 10 h prior to addition of EGF and TGF-α, completely restored EROD activity suppressed by EGF or TGF-α. However, pretreatment of tyrophostin and genistein, inhibitors of tyrosine kinase, failed to

restore the EROD activity suppressed by TGF-α. These results show that PT-sensitive G protein may play an important role in signal transduction pathway leading to suppression of P- 450 expression.

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NEWS 7	JUL 09	PATDPAFULL adds Simultaneous Left and Right Truncation (SLART) to AB, CLM, MCLM, and TI fields
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L1       17342 METABOLIZ? (3A) ENZYME

=> s l1 and (phase I or phase II)
L2        1096 L1 AND (PHASE I OR PHASE II)

=> s l2 and (transform? or transfect? or transduc?)
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L3          72 L2 AND (TRANSFORM? OR TRANSFECT? OR TRANSDUC?)

=> s l3 and adenvir?
L4           0 L3 AND ADENVIR?

=> s l3 and adenovir?
L5           0 L3 AND ADENOVIR?

=> s l3 and adeno?
L6           1 L3 AND ADENO?

=> d bib abs

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AN   2008177791  EMBASE
TI   Chemopreventive effects of Furan-2-yl-3-pyridin-2-yl-propenone
against
     7,12-dimethylbenz[a]anthracene-inducible genotoxicity.
AU   Hwang, Yong Pil; Han, Eun Hee; Choi, Jae Ho; Kim, Hyung Gyun;
Lee, Kyung
     Jin; Jeong, Hye Gwang (correspondence)
CS   BK21 Project Team, Department of Pharmacy, College of Pharmacy,
Gwangju,
     Korea, Republic of. hgjeong@chosun.ac.kr
AU   Jeong, Tae Cheon; Lee, Eung Seok
CS   College of Pharmacy, Yeungnam University, Kyungsan, Korea,
Republic of.
SO   Toxicology and Applied Pharmacology, (1 May 2008) Vol. 228, No.
3, pp.
     343-350.
     Refs: 43
     ISSN: 0041-008X  E-ISSN: 1096-0333  CODEN: TXAPA9
PUI  S 0041-008X(07)00577-7
CY   United States
DT   Journal; Article
FS   022     Human Genetics
     030     Clinical and Experimental Pharmacology
     037     Drug Literature Index
     005     General Pathology and Pathological Anatomy
     052     Toxicology
LA   English
SL   English
ED   Entered STN: 7 May 2008
     Last Updated on STN: 7 May 2008
AB   1-Furan-2-yl-3-pyridin-2-yl-propenone (FPP-3) is an
anti-inflammatory
     agent with a propenone moiety and chemically synthesized
recently.  In
     this study, we examined the chemopreventive effect of FPP-3 on
     7,12-dimethylbenz[a]anthracene (DMBA)-induced genotoxicity in
MCF-7 cells.
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FPP-3 reduced the formation of the DMBA-DNA adduct. DMBA-induced CYP1A1 and CYP1B1 gene expression and enzyme activity were inhibited by FPP-3. It inhibited DMBA-induced aryl hydrocarbon receptor (AhR) transactivation and DMBA-inducible nuclear localization of the AhR. Induction of detoxifying phase II genes by chemopreventive agents represents a coordinated protective response against oxidative stress and neoplastic effects of carcinogens. Transcription factor NF-E2 related factor 2 (Nrf2) regulates antioxidant response element (ARE) of phase II detoxifying and antioxidant enzymes, such as glutathione S-transferase (GST) and NAD(P)H:quinone oxidoreductase (QR). FPP-3 increased the expression and enzymatic activity of GST and QR. Moreover, FPP-3 increased transcriptional activity of GST and QR. GST and QR induction and Nrf2 translocation by FPP-3 were blocked by the PKC inhibitor Go6983, and the p38 inhibitor SB203580. These results reflected a partial role of PKCδ and p38 signaling in FPP-3-mediated GSTA and QR induction through nuclear translocation of Nrf2. Classically, chemopreventive agents either inhibit CYP metabolizing enzyme or induce phase II detoxifying enzymes. These results suggest that FPP-3 has a potent protective effect against DMBA-induced genotoxicity through modulating phase I and II enzymes and that it has potential as a chemopreventive agent.


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=> d his

     (FILE 'HOME' ENTERED AT 16:15:15 ON 20 AUG 2009)

     FILE 'BIOSIS, CAPLUS, EMBASE' ENTERED AT 16:15:27 ON 20 AUG 2009
L1         17342 S METABOLIZ? (3A) ENZYME
L2          1096 S L1 AND (PHASE I OR PHASE II)
L3            72 S L2 AND (TRANSFORM? OR TRANSFECT? OR TRANSDUC?)
L4             0 S L3 AND ADENVIR?
L5             0 S L3 AND ADENOVIR?
L6             1 S L3 AND ADENO?

=> dup rem l3
PROCESSING COMPLETED FOR L3
L7            58 DUP REM L3 (14 DUPLICATES REMOVED)
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=> s l7 and py<=2004
L8          34 L7 AND PY<=2004

=> y

Y IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 34 ANSWERS - CONTINUE? Y/(N):y

L8   ANSWER 1 OF 34  BIOSIS  COPYRIGHT (c) 2009 The Thomson
Corporation  on STN
AN   2004:433424  BIOSIS
DN   PREV200400435287
TI   Chemopreventive and tumoricidal properties of Ling Zhi Mushroom
Ganoderma
     lucidum (W.Curt.: Fr.)Lloyd (Aphyllophoromycetideae). Part II.
Mechanism
     considerations (Review).
AU   Gao, Yihuai; Zhou, Shufeng [Reprint Author]
CS   Dept Pharm, Natl Univ Singapore, Sci Dr 4, Singapore, 117543,
Singapore
     phazsf@nus.edu.sg
SO   International Journal of Medicinal Mushrooms, (2004) Vol. 6, No.
     3, pp. 219-230. print.
     ISSN: 1521-9437 (ISSN print).
DT   Article
     General Review; (Literature Review)
LA   English
ED   Entered STN: 10 Nov 2004
     Last Updated on STN: 10 Nov 2004
AB   We have demonstrated accumulating evidence from preclinical
(animals) and
     clinical studies that has indicated the cancer-preventive and
anticancer
     activities of Ling Zhi Mushroom (Ganoderma lucidum) in Part I.
This part
     highlights the possible underlying mechanisms involved.  Data
from a
     recent clinical study in cancer patients showed Ganopoly (a
crude G.
     lucidum polysaccharide extract) enhanced host immune function
including
     increased activity of effector cells including T lymphocytes,
macrophages,
     and natural killer cells, although striking objective antitumor
responses
     were not observed.  Currently available data from a number of in
vitro and
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in vivo studies suggests that the cancer preventive and tumoricidal properties of G. lucidum might be ascribed to its ability to enhance the host's immune functions, antioxidative and radical-scavenging effects, inhibition of metabolic activation and enhancement detoxification of carcinogens, and direct cytotoxicity. The major active constituents from G. lucidum may also exert chemopreventive and tumoricidal effects by antiproliferation and modulation of signaling transduction molecules and induction of cell-cycle arrest and apoptosis. Other mechanisms, such as anti-angiogenesis, antipromotion, and antiprogression, might also play a role. Although G. lucidum may represent a practical and promising approach for cancer prevention and cancer treatment, further studies are needed to explore the underlying mechanisms involved and identify unrevealed molecular targets.

L8 ANSWER 2 OF 34 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2004:368822 BIOSIS
DN PREV200400369761
TI Potential toxicity of flavonoids and other dietary phenolics: Significance for their chemopreventive and anticancer properties.
AU Galati, Giuseppe; O'Brien, Peter J. [Reprint Author]
CS Fac Pharm, Univ Toronto, 19 Russell St, Toronto, ON, M5S 2S2, Canada
peter.obrien@utoronto.ca
SO Free Radical Biology & Medicine, (August 1 2004) Vol. 37, No. 3, pp. 287-303. print.
ISSN: 0891-5849 (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 8 Sep 2004
Last Updated on STN: 8 Sep 2004
AB Flavonoids, including isoflavones, are natural components in our diet and, with the burgeoning interest in alternative medicine, are increasingly being ingested by the general population. Plant phenolics, which form moieties on flavonoid rings, such as gallic acid, are also widely consumed. Several beneficial properties have been attributed to these

dietary compounds, including antioxidant, anti-inflammatory, and anticarcinogenic effects. Flavonoid preparations are marketed as herbal medicines or dietary supplements for a variety of alleged nontoxic therapeutic effects. However, they have yet to pass controlled clinical trials for efficacy, and their potential for toxicity is an understudied field of research. This review summarizes the current knowledge regarding potential dietary flavonoid/phenolic-induced toxicity concerns, including their pro-oxidant activity, mitochondrial toxicity (potential apoptosis-inducing properties), and interactions with drug-metabolizing enzymes. Their chemopreventive activity in animal in vivo experiments may result from their ability to inhibit phase I and induce phase II carcinogen metabolizing enzymes that initiate carcinogenesis. They also inhibit the promotion stage of carcinogenesis by inhibiting oxygen radical-forming enzymes or enzymes that contribute to DNA synthesis or act as ATP mimics and inhibit protein kinases that contribute to proliferative signal transduction. Finally, they may prevent tumor development by inducing tumor cell apoptosis by inhibiting DNA topoisomerase 11 and p53 downregulation or by causing mitochondrial toxicity, which initiates mitochondrial apoptosis. While most flavonoids/phenolics are considered safe, flavonoid/phenolic therapy or chemopreventive use needs to be assessed as there have been reports of toxic flavonoid-drug interactions, liver failure, contact dermatitis, hemolytic anemia, and estrogenic-related concerns such as male reproductive health and breast cancer associated with dietary flavonoid/phenolic consumption or exposures.

L8 ANSWER 3 OF 34 BIOSIS
AN 2004:83217 BIOSIS
DN PREV200400069320
TI Induction of murine NAD(P)H: Quinone oxidoreductase by 2,3,7,8-tetrachlorodibenzo-p-dioxin requires the CNC (cap 'n' collar)

basic leucine zipper transcription factor Nrf2 (nuclear factor erythroid
2-related factor 2): Cross-interaction between AhR (aryl hydrocarbon
receptor) and Nrf2 signal transduction.
AU Ma, Qiang [Reprint Author]; Kinneer, Krista; Bi, Yongyi; Chan, Jefferson
Y.; Kan, Yuet Wai
CS Receptor Biology Laboratory, Toxicology and Molecular Biology Branch,
Health Effects Laboratory Division, National Institute for Occupational
Safety and Health, Centers for Disease Control and Prevention, 1095
Willowdale Road, Mail stop 3014, Morgantown, WV, 26505, USA
qam1@cdc.gov
SO Biochemical Journal, (January 2004) Vol. 377, No. 1, pp.
205-213. print.
ISSN: 0264-6021.
DT Article
LA English
ED Entered STN: 4 Feb 2004
Last Updated on STN: 4 Feb 2004
AB TCDD (2,3,7,8-tetrachlorodibenzo-p-dixoin) induces phase
II drug-metabolizing enzyme NQO1
(NAD(P)H:quinone oxidoreductase; EC 1.6.99.2; DT-diaphorase) in a wide
range of mammalian tissues and cells. Here, we analysed the molecular
pathway mediating NQO1 induction by TCDD in mouse hepatoma cells.
Inhibition of protein synthesis with CHX (cycloheximide) completely blocks
induction of NQO1 by TCDD as well as the basal expression and induction by
phenolic antioxidant tBHQ (2-t-butylbenzene-1,4-diol), implicating a
labile factor in NQO1 mRNA expression. The inhibition is both time- and
concentration-dependent, requires inhibition of protein synthesis, and
occurs at a transcriptional level. Inhibition of NQO1 transcription by
CHX correlates with a rapid reduction of the CNC bZip (cap 'n' collar
basic leucine zipper) transcription factor Nrf2 (nuclear factor erythroid
2-related factor 2) through the 26 S proteasome pathway. Moreover,
blocking Nrf2 degradation with proteasome inhibitor MG132 increases the
amount of Nrf2 and superinduces NQO1 in the presence of TCDD or tBHQ.

Finally, genetic experiments using AhR (aryl hydrocarbon receptor)-, Arnt (aryl hydrocarbon receptor nuclear translocator)- or Nrf2-deficient cells reveal that, while induction of NQO1 by TCDD depends on the presence of AhR and Arnt, the basal and inducible expression of NQO1 by either TCDD or tBHQ requires functional Nrf2. The findings demonstrate a novel role of Nrf2 in the induction of NQO1 by TCDD and provide new insights into the mechanism by which Nrf2 regulates the induction of phase II enzymes by both phenolic antioxidants and AhR ligands.

L8 ANSWER 4 OF 34 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 2000:68221 BIOSIS
DN PREV200000068221
TI DT-diaphorase expression and tumor cell sensitivity to 17-allylamino,17-demethoxygeldanamycin, an inhibitor of heat shock protein 90.
AU Kelland, Lloyd R.; Sharp, Swee Y.; Rogers, Paul M.; Myers, Timothy G.; Workman, Paul [Reprint author]
CS Cancer Research Campaign Centre for Cancer Therapeutics, The Institute of Cancer Research, 15 Cotswold Rd., Sutton, Surrey, SM2 5NG, UK
SO Journal of the National Cancer Institute (Bethesda), (Nov. 17, 1999) Vol. 91, No. 22, pp. 1940-1949. print.
CODEN: JNCIEQ. ISSN: 0027-8874.
DT Article
LA English
ED Entered STN: 9 Feb 2000
Last Updated on STN: 3 Jan 2002
AB Background: To our knowledge, 17-allylamino, 17-demethoxygeldanamycin (17AAG) is the first inhibitor of heat shock protein 90 (Hsp90) to enter a phase I clinical trial in cancer. Inhibition of Hsp90, a chaperone protein (a protein that helps other proteins avoid misfolding pathways that produce inactive or aggregated states), leads to depletion of important oncogenic proteins, including Raf-1 and mutant p53 (also known as TP53). Given its ansamycin benzoquinone structure, we questioned whether the antitumor activity of 17AAG was affected by expression of the NQO1 gene, which encodes the quinone-metabolizing enzyme

DT-diaphorase. Methods: The antitumor activity of 17AAG and other Hsp90 inhibitors was determined by use of a sulforhodamine B-based cell growth inhibition assay in culture and by the arrest of xenograft tumor growth in nude mice. DT-diaphorase activity was determined by use of a spectrophotometric assay, and protein expression was determined by means of western immunoblotting. Results: In two independent in vitro human tumor cell panels, we observed a positive relationship between DT-diaphorase expression level and growth inhibition by 17AAG. Stable, high-level expression of the active NQO1 gene transfected into the DT-diaphorase-deficient (by NQO1 mutation) BE human colon carcinoma cell line resulted in a 32-fold increase in 17AAG growth-inhibition activity. Increased sensitivity to 17AAG in the transfected cell line was also confirmed in xenografts. The extent of depletion of Raf-1 and mutant p53 protein confirmed that the Hsp90 inhibition mechanism was maintained in cells with high and low levels of DT-diaphorase. 17AAG was shown to be a substrate for purified human DT-diaphorase. Conclusion: These results suggest that the anti-tumor activity and possibly the toxicologic properties of 17AAG in humans may be influenced by the expression of DT-diaphorase. Careful monitoring for NQO1 polymorphism and the level of tumor DT-diaphorase activity is therefore recommended in clinical trials with 17AAG.

L8 ANSWER 5 OF 34 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
AN 1999:444548 BIOSIS
DN PREV199900444548
TI 1998 Annual Meeting of the Society of Toxicology Symposium on characterization of xenobiotic metabolizing enzyme function using heterologous expression systems (Seattle, Washington, USA).
AU Townsend, Alan J. [Reprint author]; Kiningham, Kinsley K.; St. Clair, Daret; Tephly, Thomas R.; Morrow, Charles S.; Guengerich, F. Peter
CS Department of Biochemistry, Wake Forest University School of Medicine,

Winston-Salem, NC, 27157, USA
SO Toxicological Sciences, (April, 1999) Vol. 48, No. 2, pp. 143-150. print.
ISSN: 1096-6080.
DT Conference; (Meeting)
Conference; Report; (Meeting Report)
LA English
ED Entered STN: 26 Oct 1999
Last Updated on STN: 3 May 2000
AB Genetically modified cell lines can be very useful models for assessing the toxicologic effects of modulation of expression of individual gene products in comparison to their isogenic parental control cell lines. This symposium begins with an overview of general issues related to development and utilization of model systems created by transfection of cell lines to induce elevated expression of metabolic enzymes of toxicologic relevance. Selected studies that illustrate the heterologous expression rationale and various approaches to transgenic-cell model construction are represented. Results to date with cells engineered to express specific transfected genes are discussed, with emphasis on the effects of expression of selected phase I or phase II enzymes on cellular sensitivity to several toxic end-points. The individual sections highlight the utility of these model cell lines for examining the role of enzyme catalysis and function in metabolism of biologically active xenobiotic or endobiotic compounds of interest in toxicology. Both activating and detoxifying enzymes are discussed, with principal emphasis on the latter. This symposium includes talks on transfected cells that express aldehyde dehydrogenases, superoxide dismutase, UDP-glycosyltransferases, glutathione transferases, and cytochrome P450 isozymes. In addition to the general toxicologic utility and advantages of these genetically engineered cell lines, this overview emphasizes their particular contributions to the insights obtained to date with the specific model cell lines.

L8 ANSWER 6 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2003:739062 CAPLUS

DN 140:230825
TI Interactions of paralytic shellfish toxins with xenobiotic-metabolizing and antioxidant enzymes in rodents
AU Hong, Hai-zheng; Lam, Paul K. S.; Hsieh, Dennis P. H.
CS Department of Biology, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, Peop. Rep. China
SO Toxicon (2003), 42(4), 425-431
CODEN: TOXIA6; ISSN: 0041-0101
PB Elsevier Science B.V.
DT Journal
LA English
AB Paralytic shellfish toxins (PSTs) are neurotoxins known to block voltage-gated sodium channels in intoxicated animals and humans. Their metabolism in mammalian systems and their effects on other receptors are not as well understood. In this study, we investigated the in vitro metabolism of two classes of PSTs, gonyautoxin 2/3 (GTX2/3) and C1/2 toxins (C1/2), using rat and mouse liver enzyme prepns. We also analyzed the effects of these toxins on several antioxidant and xenobiotic-metabolizing enzymes in mice. These toxins were selected for their prevalence in the coastal waters of Southern China. When the toxins were incubated with liver prepns. containing Phase I and Phase II xenobiotic metabolizing enzymes and appropriate co-factors, no transformation of the toxins was detectable. When mice were given sub-LDs of GTX2/3, a loss of activity was observed in hepatic ethoxyresorufin-O-deethylase, pentoxyresorufin-O-deethylase, glutathione peroxidase and superoxide dismutase, but not in glutathione S-transferase, catalase and glutathione reductase. Exposure to the same mouse units of C1/2 caused only a slight reduction in the activity of penthoxyresorufin-O-deethylase and glutathione peroxidase. Our results indicated that these toxins may not be metabolized readily in mammals and that they may cause adverse effects other than sodium channel blocking.
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2003:78734 CAPLUS
DN 138:349784
TI Cancer and phase II drug-metabolizing enzymes
AU Sheweita, S. A.; Tilmisany, A. K.
CS Department of Bioscience & Technology, Institute of Graduate Studies &
Research, Alexandria University, Egypt
SO Current Drug Metabolism (2003), 4(1), 45-58
CODEN: CDMUBU; ISSN: 1389-2002
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Cancer development results from the interaction between genetic
factors and the environment, and dietary factors have been identified as
modulators of the carcinogenesis process. The formation of DNA adducts is
recognized as the initial step in chemical carcinogenesis. Accordingly,
blocking DNA adducts formation would be the first line of defense against
cancer caused by carcinogens. Glutathione S-transferases inactivate chemical
carcinogens into less toxic or inactive metabolites through the reduction of
DNA adducts formation. There are many different types of glutathione
S-transferase isoenzymes. For example, GSTπ serves as a marker for
hepatotoxicity in the rodent system, and also plays an important role in
carcinogen detoxification. Therefore, inhibition of GST activity might
potentiate the deleterious effects of many environmental toxicants and
carcinogens. In addition, approx. half of the population lacks GST Mu
expression. Epidemiol. evidence showed that persons possessing this
genotype are predisposed to a number of cancers including breast, prostate,
liver, and colon cancers. In addition, the individual risk of cancer depends
on the frequency of mutational events in target oncogenes and tumor
suppressor genes which could lead to the loss of chromosomal materials and
tumor progression. The most frequent genetic alteration in a variety of

human malignant tumors is the mutation of the coding sequence of the p53 tumor suppressor gene. O6-alkylguanine in DNA leads to very high rates of G:C→A:T transitions in p53 gene. These alterations will modulate the expression of p53 gene and consequently change DNA repair, cell division, and cell death by apoptosis. Also, changes in the expression of BcI-2 gene results in extended viability of cells by overriding programmed cell death (apoptosis) induced under various conditions. The prolonged life span increases the risk of acquiring genetic changes resulting in malignant transformation. In addition, a huge variety of food ingredients have been shown to affect cell proliferation rates. They, therefore, may either reduce or increase the risk of cancer development and progression. For example, it has been found that a high intake of dietary fat accelerates the development of breast cancer in animal models. Certain diets have been suggested to act as tumor promoters also in other types of cancer such as colon cancer, where high intake of fat and phosphate have been linked to colonic hyper-proliferation and colon cancer development. Different factors such as oncogenes, aromatic amines, alkylating agents, and diet have a significant role in cancer induction. Determination of glutathione S-transferase isoenzymes in plasma or serum could be used as a biomarker for cancer in different organs and could give an early detection.

OSC.G 45 THERE ARE 45 CAPLUS RECORDS THAT CITE THIS RECORD (45 CITINGS)
RE.CNT 221 THERE ARE 221 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2002:737245 CAPLUS
DN 138:280595
TI Pharmacogenomics, regulation and signaling pathways of phase I and II drug metabolizing enzymes
AU Rushmore, Thomas H.; Kong, A.-N. Tony
CS Department of Drug Metabolism, Merck Research Laboratory, West Point, PA,

USA
SO Current Drug Metabolism (2002), 3(5), 481-490
CODEN: CDMUBU; ISSN: 1389-2002
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Drug or xenobiotics metabolizing enzymes (DMEs or XMEs) play central roles in the biotransformation, metabolism and/or detoxification of xenobiotics or foreign compds., that are introduced to the human body. In general, DMEs protect or defened the body against the potential harmful insults from the environment. Once in the body, many xenobiotics may induce signal transduction events either specifically or non-specifically leading to various cellular, physiol. and pharmacol. responses including homeostasis, proliferation, differentiation, apoptosis, or necrosis. For the body to minimize the insults caused by these xenobiotics, various tissues / organs are well equipped with diverse DMEs including various Phase I and Phase II enzymes, which are present in abundance either at the basal level and/or increased / induced after exposure. To better understand the pharmacogenomic/gene expression profile of DMEs and the underlying mol. mechanisms after exposure to xenobiotics or drugs, we will review our current knowledge on DNA microarray technol. in gene expression profiling and the signal transduction events elicited by various xenobiotics mediated by either specific receptors or non-specific signal transduction pathways. Pharmacogenomics is the study of genes and the gene products (proteins) essential for pharmacol. or toxicol. responses to pharmaceutical agents. In order to assess the battery of genes that are induced or repressed by xenobiotics and pharmaceutical agents, cDNA microarray or oligonucleotide-based DNA chip technol. can be a powerful tool to analyze, simultaneously, the gene expression profiles that are induced or repressed by xenobiotics. The regulation of gene expression of the various phase I DMEs such as the cytochrome P 450 (CYP) as well as phase II DMEs

generally depends on the interaction of the xenobiotics with the receptors. For instance, the expression of CYP1 genes can be induced via the aryl hydrocarbon receptor (AhR) which dimerizes with the AhR nuclear translocator (ARNT), in response to many polycyclic aromatic hydrocarbon (PAHs). Similarly, the steroid family of orphan receptors, the constitutive androstane receptor (CAR) and pregnane X receptors (PXR), heterodimerize with the retinoid X receptor (RXR), transcriptionally activate the promoters of CYP2B and CYP3A gene expression by xenobiotics such as phenobarbital-like compds. (CAR) and dexamethasone and rifampin-type of agents (PXR). The peroxisome proliferator activated receptor (PPAR) which is one of the first characterized members of the nuclear hormone receptor, also dimerizes with RXR and it has been shown to be activated by lipid lowering agent fibrate-type of compds. leading to transcriptional activation of the promoters on the CYP4A genes. The transcriptional activation of these promoters generally leads to the induction of their mRNA. The physiol. and the pharmacol. implications of common partner of RXR for CAR, PXR, and PPAR receptors largely remain unknown and are under intense investigations. For the phase II DMEs, phase II gene inducers such as phenolic compds. butylated hydroxyanisol (BHA), tert-butylhydroquinone (tBHQ), green tea polyphenol (GTP), (-)-epicatechin-3-gallate (EGCG) and the isothiocyanates (PEITC, sulforaphane) generally appear to be electrophiles. They can activate the mitogen-activated protein kinase (MAPK) pathway via electrophilic-mediated stress response, resulting in the activation of bZIP transcription factors Nrf2 which dimerizes with Mafs and binds to the antioxidant/electrophile response element (ARE/EpRE) enhancers which are found in many phase II DMEs as well as many cellular defensive enzymes such as thioredoxins, γGCS and HO-I, with the subsequent induction of gene expression of these genes.

It appears that in general, exposure to phase I or

phase II gene inducers or xenobiotics may trigger a cellular "stress" response leading to the increase in the gene expression of these DMEs, which ultimately enhance the elimination and clearance of the xenobiotics and/or the "cellular stresses" including harmful reactive intermediates such as reactive oxygen species (ROS), so that the body will remove the "stress" expeditiously. Consequently, this homeostatic response of the body plays a central role in the protection of the organism against environmental insults such as xenobiotics. Advances in DNA microarray technologies and mammalian genome sequencing will soon allow quant. assessment of expression profiles of all genes in the selected tissues. The ability to predict phenotypic outcomes from gene expression profiles is currently in its infancy, however, and will require addnl. bioinformatic tools. Such tools will facilitate information gathering from literature and gene databases as well as integration of expression data with animal physiol. studies. The study of pharmacogenomic/gene expression profile and the understanding of the regulation and the signal transduction mechanisms elicited by pharmaceutical agents can be of potential importance during drug discovery and the drug development.

OSC.G 133 THERE ARE 133 CAPLUS RECORDS THAT CITE THIS RECORD (133 CITINGS)

RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2002:691294 CAPLUS

DN 137:347760

TI Decreased hepatic drug metabolising enzyme activity in rats with nitrosamine-induced tumours

AU Maliakal, P. P.; Coville, P. F.; Wanwimolruk, S.

CS School of Pharmacy, University of Otago, Dunedin, N. Z.

SO Drug Metabolism and Drug Interactions (2002), 19(1), 13-27
CODEN: DMDIEQ; ISSN: 0792-5077

PB Freund Publishing House Ltd.

DT Journal

LA English

AB N-Me N-benzyl nitrosamine (MBNA), which requires P 450-dependent

activation to be mutagenic, has been shown to produce squamous cell carcinoma of rat esophagus. The aim of this study was to determine the effects of tumor induction on hepatic cytochrome P 450 (CYP) and phase II enzyme activity. Female Wistar rats were given MBNA (2.5 mg/kg) by gavage, twice weekly for 12 wk. At the end of 12 wk they were sacrificed; livers and esophagi were removed. The activity of hepatic CYP and phase II enzymes was determined by incubation of liver microsomes with appropriate CYP substrates. All rats receiving MBNA developed esophageal lesions. Hepatic CYP1A2 activity (phenacetin 5 μM) in tumor-bearing rats was significantly decreased to 53% of the controls ($p < 0.05$). CYP2E1 (p-nitrophenol hydroxylase), CYP2D (debrisoquine hydroxylase) and CYP3A (quinine hydroxylase) activity was significantly ($p < 0.05$) reduced. Microsomal UDP-glucuronosyl transferase activity was also found to be markedly decreased while glutathione-S-transferase activity remained almost unchanged. Alteration of the activities of drug metabolizing enzymes in rats with chemical induced tumors could be an important factor in determining resistance or susceptibility to xenobiotics and antitumor drugs.

OSC.G 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2001:839513 CAPLUS

DN 137:58864

TI Comparison of the levels of enzymes involved in drug metabolism between transgenic or gene-knockout and the parental mice

AU Ariyoshi, Noritaka; Imaoka, Susumu; Nakayama, Kazuo; Takahashi, Yoshiki; Fujita, Ken-Ichi; Funae, Yoshihiko; Kamataki, Tetsuya

CS Laboratory of Drug Metabolism, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060-0812, Japan

SO Toxicologic Pathology (2001), 29(Suppl.), 161-172
CODEN: TOPADD; ISSN: 0192-6233

PB Society of Toxicologic Pathologists

DT Journal

LA English

AB Drug-metabolizing enzymes are involved in the metabolic activation or detoxification of carcinogens. To evaluate animals developed as models for alternative carcinogenicity testing, the authors investigated whether or not a gene manipulation including the transgene of ras and the knocking out of a tumor suppressor gene such as p53 or XPA could alter the expression of representative drug-metabolizing enzymes directly or indirectly. Expression of several isoforms of cytochrome P 450 (CYP) in the liver of rasH2, p53 (+/-), Tg.AC, and XPA (-/-) mice with or without treatment of prototype inducer, phenobarbital or 3-methylcholanthrene, was analyzed by Western immunoblotting in comparison with their parental strains of mice. In addition, the activities of 3 major phase II enzymes, UDP-glucuronosyltransferase, sulfotransferase, and glutathione S-transferase, were compared between the gene-manipulated and the corresponding parental strains of mice. Results demonstrate that XPA gene knockout appeared to increase constitutive expression of CYP2B and CYP3A isoforms. Over-expression of human c-Ha-ras gene or p53 gene knockout appeared to increase constitutive UGT activity toward 4-nitrophenol. The content or activities of almost all other enzymes examined in the present study do not appear to be affected by the gene manipulation.
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2001:591757 CAPLUS
DN 136:31135
TI Signal transduction events elicited by cancer prevention compounds
AU Kong, A.-N. T.; Yu, R.; Hebbar, V.; Chen, C.; Owuor, E.; Hu, R.; Ee, R.; Mandlekar, S.
CS Department of Pharmaceutics and Pharmacodynamics, Center for Pharmaceutical Biotechnology, MC 870, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, 60607, USA

SO Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis (
2001), 480-481, 231-241
CODEN: MUREAV; ISSN: 0027-5107
PB Elsevier Science B.V.
DT Journal; General Review
LA English
AB A review is given. Many chemopreventive agents were shown to modulate
gene expression including induction of phase II
detoxifying enzymes, such as glutathione S-transferases (GST) and quinone
reductases (QR). Induction of phase II enzymes in
general leads to protection of cells/tissues against exogenous and/or
endogenous carcinogenic intermediates. The antioxidant or electrophile
response element (ARE/EpRE) found at the 5'-flanking region of these
phase II genes may play important role in mediating
their induction by xenobiotics including chemopreventive agents. Members
of the basic Leu zipper (bZIP) transcription factor, Nrf2 which
heterodimerizes with Maf G/K, are found to bind to the ARE, and
transcriptionally-activated ARE. Recently, the authors showed that the
mitogen-activated protein kinases (MAPK) were activated by phase
II gene inducers such as phenolic antioxidant butylated
hydroxyanisol (BHA) and isothiocyanate sulforaphane (SUL), and involved in
the transcription activation of ARE-mediated reporter gene.
Transfection studies with wild-type and dominant neg. mutants of
Nrf2 and MAPK showed synergistic response during co-transfection
as well as to phase II gene inducers. However,
increasing the concns. of these compds. such as BHA, the activities of
cell death signaling mols., caspases, were stimulated and resulted in
apoptotic cell death. At these concns., BHA stimulated loss of
mitochondrial membrane potential, cytochrome c release, and activation of
caspase 3, 8, and 9 preceding apoptosis. Further increase in concns. led
to rapid cell necrosis. A model is proposed for BHA and SUL, in that at
low concns., these potential chemopreventive agents may modulate MAPK
pathway leading to transcription activation of Nrf2 and ARE with
subsequent induction of cellular defensive enzymes including phase
II detoxifying enzymes as well as other defensive genes, which may

protect the cells against cellular injury, which is a homeostatic response. At higher concns., these agents may activate the caspase pathways, leading to apoptosis, a potential beneficial effect if occurs at preneoplastic/neoplastic tissues, but a potential cytotoxic response if occurs in normal tissues. On the other hand, some phenolic compds. such as resveratrol inhibits TPA- or UV-induced AP-1-mediated activity through the inhibition of c-Src non-receptor tyrosine kinase and MAPK pathways. It is possible that in proliferating or stimulated cells, these chemopreventive compds. may block proliferation by inhibiting these signaling kinases, whereas in non-proliferating or quiescent cells, some of these compds. may activate these signaling kinases leading to gene expression of cellular defensive enzymes such as phase II detoxifying enzymes. The studies of these and other signaling pathways may yield insights into the development of potential chemopreventive compds.

OSC.G 64 THERE ARE 64 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)

RE.CNT 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN

AN 1999:129561 CAPLUS

DN 131:15

TI New strategies for cancer treatment by gene therapy and chemotherapy combination

AU Wu, De-Zheng

CS Affiliated Hospital, Academy of Military Medical Sciences, Beijing, 100850, Peop. Rep. China

SO Zhongguo Linchuang Yaolixue Zazhi (1998), 14(1), 48-52, 61
CODEN: ZLYZE9; ISSN: 1001-6821

PB Zhongguo Yaoxuehui

DT Journal; General Review

LA Chinese

AB A review with 24 refs. Because the relevant technol. of gene therapy and the transfection efficiency has been improved recently more than 100 protocols of gene therapy for cancer have been put into phase I/II clin. trials and promising results have obtained. This article mainly reviews the development in combination use of gene therapy and chemotherapy to improve the selectivity of chemotherapeutic agents.

The following protocols were introduced. Herpes simplex thymidine kinase gene/ganciclovir combination protocol, cytosine deaminase gene/ 5-fluorocytosine protocol, cytochrome P450 gene (CYP)/ oxazaphosphorines protocol. The principles of above three protocols were similar. The prodrug metabolizing enzyme gene was transfected to the tumor cells only. After gene transfection of tumor cells (not to normal host tissues) the prodrug administered could be activated and the cytocidal effect was produced only in the tumor. No cytotoxic effect was produced in normal host tissues. 4. Mdr1 gene transfected to bone marrow cells in combination use of chemotherapeutic agent protocol. Above protocols showed that gene therapy may provide a novel approach for the improvement of selectivity of chemotherapeutic agents.

L8 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1997:761501 CAPLUS
DN 128:31327
OREF 128:6060h,6061a
TI Cancer chemoprevention from the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine: reconsideration of the evidence
AU Paolini, M.; Biagi, G. L.; Cantelli-Forti, G.
CS Biochemical Toxicology Unit, Department of Pharmacology, University of Bologna, Bologna, 40126, Italy
SO Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis (1997), 381(2), 279-282
CODEN: MUREAV; ISSN: 0027-5107
PB Elsevier Science B.V.
DT Journal
LA English
AB It should be considered that metaboling enzymes are upstream in the regulatory cascade of numerous transduction signal pathways that have a fundamental role in maintenance of steady state levels of specific endogenous ligands in cells. Once again, it is evident that preventive modulation of these enzymes alters the correlated physiol. functions (growth, apoptosis, differentiation, homeostasis etc.). On the whole, from these considerations it appears that any attempt to modulate each

metabolizing enzyme reaction rate of either
phase I or phase II by dietary
component (including drugs) to reduce cancer risk in humans should be
carefully considered.
OSC.G 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1997:71620 CAPLUS
DN 126:180907
OREF 126:34761a,34764a
TI Cancer chemopreventive potential of sulforamate, a novel analog of
sulforaphane that induces phase 2 drug-metabolizing enzymes
AU Gerhauser, Clarissa; You, Min; Liu, Jinfang; Moriarty, Robert M.;
Hawthorne, Michael; Mehta, Rajendra G.; Moon, Richard C.; Pezzuto, John M.
CS Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy,
University of Illinois at Chicago, Chicago, IL, 60612, USA
SO Cancer Research (1997), 57(2), 272-278
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Chemoprevention involves the use of natural or synthetic substances to
reduce the risk of developing cancer. Two dietary components capable of
mediating chemopreventive activity in animal models by modulation of
drug-metabolizing enzymes are sulforaphane, an aliphatic isothiocyanate, and
brassinin, an indole-based dithiocarbamate, both found in cruciferous
vegetables. The authors currently report the synthesis and activity of a
novel cancer chemopreventive agent,
(±)-4-methylsulfinyl-1-(S-methyldithiocarbamyl)-butane (trivial name,
sulforamate), an aliphatic analog of brassinin with structural similarities
to sulforaphane. This compound was shown to be a monofunctional inducer of
NAD(P)H:quinone oxidoreductase [quinone reductase (QR)], a Phase
II enzyme, in murine Hepa 1c1c7 cell culture and two mutants
thereof. Induction potential was comparable to that observed with
sulforaphane (concentration required to double the specific activity of QR,

.apprx.0.2 μM), but cytotoxicity was reduced by about 3-fold (IC50
.apprx.30 μm). In addition, sulforaphane, as well as the analog,
increased glutathione levels about 2-fold in cultured Hepa 1c1c7 cells.
Induction of QR was regulated at the transcriptional level. Using
Northern blotting techniques, time- and dose-dependent induction of QR
mRNA levels were demonstrated in Hepa 1c1c7 cell culture. To further
investigate the mechanism of induction, HepG2 human hepatoma cells were
transiently transfected with QR-chloramphenicol
acetyltransferase plasmid constructs containing various portions of the
5'-region of the QR gene. Sulforaphane and the analog significantly
induced CAT activity at a concentration of 12.5 μM by interaction with the
antioxidant responsive element (5-14-fold induction) without interacting
with the xenobiotic responsive element. Moreover, both compds.
significantly induced mouse mammary QR and glutathione S-transferase
activity (feeding of 3 mg/mouse intragastric for 4 days), whereas the
elevation of hepatic enzyme activities was less pronounced. Both
sulforaphane and the analog were identified as potent inhibitors of
preneoplastic lesion formation in carcinogen-treated mouse mammary glands
in organ culture (84% and 78% inhibition at 1 μm, resp.). On the basis
of these results, the sulforaphane analog can be regarded as a readily
available promising new cancer chemopreventive agent.
OSC.G 153 THERE ARE 153 CAPLUS RECORDS THAT CITE THIS RECORD (154 CITINGS)
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 34 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1989:171009 CAPLUS
DN 110:171009
OREF 110:28329a,28332a
TI Profile of drug metabolizing enzymes in the nuclear and microsomal
fractions from rat liver nodules and normal liver
AU Pacifici, G. M.; Eriksson, L. C.; Glaumann, H.; Rane, A.
CS Div. Clin. Pharmacol., Univ. Hosp., Uppsala, S-751 85, Swed.

SO Archives of Toxicology (1988), 62(5), 336-40
CODEN: ARTODN; ISSN: 0340-5761
DT Journal
LA English
AB The activities of UDP-glucuronyl transferase, DT-diaphorase, epoxide hydrolase, aryl hydrocarbon hydroxylase, γ-glutamyl transferase, and NADPH-cytochrome c reductase were measured in the nuclear and microsomal fractions from normal rat liver and rat liver preneoplastic nodules. Nodules were produced by intermittent feeding of Wistar rats with a standard diet supplemented with 0.05% 2-acetylaminofluorene. The activities of UDP-glucuronyl transferase, DT-diaphorase, epoxide hydrolase and γ-glutamyl transferase were increased in the nuclear and microsomal fractions obtained from nodules as compared with normal liver. Aryl hydrocarbon hydroxylase activity was decreased in the microsomal fraction from the pathol. tissue but not in the nuclear fraction. NADPH-cytochrome c reductase activity was similar in nodular and normal liver tissue. The nuclear/microsomal ratio for phase I reactions in xenobiotic metabolism was increased over normal >2-fold. Thus, the nuclear and microsomal systems for drug metabolism are both changed in liver nodules. The relative enhancement of nuclear activating reactions is remarkable in the light of the increased risk for malignant transformation exhibited by nodular cells.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L8 ANSWER 16 OF 34 EMBASE
AN 2004510542 EMBASE
TI The human sulfotransferase SULT1A1 gene is regulated in a synergistic manner by Sp1 and GA binding protein.
AU Hempel, Nadine; McManus, Michael E., Dr. (correspondence)
CS Dept. of Physiology and Pharmacology, School of Biomedical Sciences, University of Queensland, Brisbane, QLD, Australia. m.mcmanus@uq.edu.au
AU Wang, Hongbing; LeCluyse, Edward L.

CS Div. of Drug Delivery/Disposition, School of Pharmacy, University of North
Carolina, Chapel Hill, NC, United States.
AU Hempel, Nadine; Negishi, Masahiko
CS Pharmacogenetics Section, Lab. of Repro. and Devmtl. Toxicol., Natl. Inst.
of Environ. Hlth. Sci., Research Triangle Park, NC, United States.
AU McManus, Michael E., Dr. (correspondence)
CS Fac. of Biol. and Chemical Sciences, University of Queensland, Brisbane,
QLD 4072, Australia. m.mcmanus@uq.edu.au
SO Molecular Pharmacology, (Dec 2004) Vol. 66, No. 6, pp. 1690-1701.
Refs: 40
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
LA English
SL English
ED Entered STN: 28 Dec 2004
Last Updated on STN: 28 Dec 2004
AB Human sulfotransferase SULT1A1 is an important phase II xenobiotic metabolizing enzyme that is highly expressed in the liver and mediates the sulfonation of drugs, carcinogens, and steroids. Until this study, the transcriptional regulation of the SULT1A subfamily had been largely unexplored. Preliminary experiments in primary human hepatocytes showed that SULT1A mRNA levels were not changed in response to nuclear receptor activators, such as dexamethasone and 3-methylcolanthrene, unlike other metabolizing enzymes. Using HepG2 cells, the high activity of the TATA-less SULT1A1 promoter was shown to be dependent on the presence of Sp1 and Ets transcription factor binding sites (EBS), located within -112 nucleotides from the transcriptional start site. The homologous promoter of the closely related SULT1A3 catecholamine sulfotransferase, which is expressed at negligible levels in the adult liver, displayed 70% less activity than SULT1A1. This was shown to be caused by a two-base pair difference in the EBS. The Ets transcription factor GA binding protein (GABP) was shown to bind the

SULT1A1 EBS and could transactivate the SULT1A1 promoter in Drosophila melanogaster S2 cells. Cotransfection of Sp1 could synergistically enhance GABP-mediated activation by 10-fold. Although Sp1 and GABP alone could induce SULT1A3 promoter activity, the lack of the EBS on this promoter prevented a synergistic interaction between the two factors. This study reports the first insight into the transcriptional regulation of the SULT1A1 gene and identifies a crucial difference in regulation of the closely related SULT1A3 gene, which accounts for the two enzymes' differential expression patterns observed in the adult liver.

L8 ANSWER 17 OF 34 EMBASE

AN 2004344170 EMBASE

TI Effect of bisphenol A on drug metabolising enzymes in rat hepatic microsomes and precision-cut rat liver slices.

AU Pfeiffer, Erika; Metzler, Manfred (correspondence)

CS Inst. of Food Chem. and Toxicology, University of Karlsruhe, P.O. Box 6980, D-76128 Karlsruhe, Germany. manfred.metzler@chemie.uni-karlsruhe.de

SO Archives of Toxicology, (Jul 2004) Vol. 78, No. 7, pp. 369-377. Refs: 23 ISSN: 0340-5761 CODEN: ARTODN

CY Germany

DT Journal; Article

FS 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
048 Gastroenterology
005 General Pathology and Pathological Anatomy
052 Toxicology

LA English

SL English

ED Entered STN: 2 Sep 2004
Last Updated on STN: 2 Sep 2004

AB In order to assess the effects of bisphenol A (BPA) on enzymes of phase I and II biotransformation, studies were conducted in hepatic microsomes and precision-cut liver slices from male Sprague-Dawley rats. A testosterone hydroxylation assay was used for probing the activity of cytochrome P450 (CYP) forms, and an appropriate HPLC method for the separation of testosterone metabolites was developed.

BPA markedly inhibited the hydroxylation of testosterone at 2α and 16α but not at 6β or 7α, suggesting a differential inhibition of some CYP forms, in particular CYP2C11. This inhibitory effect was also observed when slices were first exposed to BPA and then incubated with testosterone in the absence of BPA, indicative of an irreversible inhibition of CYP. In liver slices, a differential conjugation of hydroxylated testosterone metabolites was observed, which was significantly decreased in the presence of BPA. BPA also inhibited the conjugation of the model compound umbelliferone. Pretreatment with BPA did not affect the conjugation of testosterone and umbelliferone. No hydroxylation, but extensive conjugation of BPA was observed upon incubation of liver slices with BPA alone or with testosterone or umbelliferone. The rapid and preferred conjugation, however, does not prevent the irreversible inhibition of some CYP forms by BPA. In conclusion, this study has shown that BPA causes a selective and irreversible inhibition of certain CYP forms and interferes with the conjugation of other drugs. .COPYRGT. Springer-Verlag 2004.

L8 ANSWER 18 OF 34 EMBASE

AN 2004223738 EMBASE

TI Zerumbone, a sesquiterpene in subtropical ginger, suppresses skin tumor initiation and promotion stages in ICR mice.

AU Murakami, Akira (correspondence); Kim, Ha Won; Kawabata, Kyuichi; Ohigashi, Hajime

CS Div. of Food Sci. and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto 606-8502, Japan. cancer@kais.kyoto-a.ac.jp

AU Tanaka, Takuji

CS First Department of Pathology, Kanazawa Medical University, Uchiinada, Ishikawa, Japan.

AU Lee, Ji-Yoon; Surh, Young-Joon

CS College of Pharmacy, Seoul National University, Shinlim-dong, Kwanak-ku, Seoul, Korea, Republic of.

AU Nakamura, Yoshimasa

CS Laboratory of Food and Biodynamics, Nagoya University, Grad. Sch. of Bioagricultural Sci., Nagoya, Japan.

AU Jiwajinda, Suratwadee
CS Environmental Science Unit, Ctrl. Lab. and Greenhouse Complex, Kasetsart
University, Nakorn-Pathom, Thailand.
SO International Journal of Cancer, (1 Jul 2004) Vol. 110, No. 4, pp.
481-490.
Refs: 75
ISSN: 0020-7136 CODEN: IJCNAW
CY United States
DT Journal; Article
FS 013 Dermatology and Venereology
016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 10 Jun 2004
Last Updated on STN: 10 Jun 2004
AB We recently showed that zerumbone, a sesquiterpene found in subtropical
ginger, suppresses colonic tumor marker formation in rats and induces
apoptosis in colon cancer cell lines. In our present study, the
anti-tumor initiating and promoting activities of zerumbone in mouse skin
were evaluated using a conventional 2-stage carcinogenesis model. A
single topical pretreatment to mouse skin (2 μmol) 24 hr before
application of dimethylbenz[a]anthracene (0.2 μmol) markedly suppressed
tumor incidence by 60% and the number of tumors by 80% per mouse.
Repeated pretreatment (16 nmol) twice weekly during the post-initiation
phase reduced the number of 12-O-tetradecanoylphorbol-13-acetate (TPA, 1.6
nmol)-induced tumors by 83% as well as their diameter by 57%. Multiple
reverse transcriptase (RT) PCR experiments revealed that zerumbone (2
μmol) enhanced the mRNA expression level of manganese superoxide
dismutase, glutathione peroxidase-1, glutathione S-transferase-PI and
NAD(P)H quinone oxidoreductase in the epidermis, but not that of
cytochrome P450 1A1 or 1B1. Further, it diminished TPA-induced
cyclooxygenase-2 protein expression and phosphorylation of extracellular
signal-regulated kinase 1/2, while pretreatment(s), in either the priming
or activation stage or both, reduced double TPA application-induced
hydrogen peroxide formation and edema induction by 29% to 86%,

respectively. Histologic examination revealed that pretreatment(s) with zerumbone suppressed leukocyte infiltration and reduced proliferating cell nuclear antigen-labeling indices. Together, our results indicate that zerumbone is a promising agent for the prevention of both tumor initiating and promoting processes, through induction of anti-oxidative and phase II drug metabolizing enzymes as well as attenuation of proinflammatory signaling pathways. .COPYRGT. 2004 Wiley-Liss, Inc.

L8 ANSWER 19 OF 34 EMBASE
AN 2004009096 EMBASE
TI Conjugation metabolism of acetaminophen and bilirubin in extrahepatic tissues of rats.
AU Li, X.D.; Xia, S.Q.; Lv, Y.; He, P. (correspondence); Han, J.; Wu, M.C.
CS E. Hepatobiliary Surgery Institute, Second Military Medical University, Shanghai 200438, China.
SO Life Sciences, (23 Jan 2004) Vol. 74, No. 10, pp. 1307-1315.
Refs: 21
ISSN: 0024-3205 CODEN: LIFSAK
CY United States
DT Journal; Article
FS 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 22 Jan 2004
Last Updated on STN: 22 Jan 2004
AB An anhepatic rat model was used to explore the extrahepatic conjugating metabolism of acetaminophen and serum bilirubin. The recovery of glucuronide- and sulfate-acetaminophen was 47.5% in normal control and 13.4% in model rats in the urine collected for 6 h after administration of acetaminophen 20 mg kg(-1). Following the increase of acetaminophen dose to 150 mg kg (-1), the recovery of urinary glucuronide-acetaminophen increased by 53.9% in normal control; but it decreased by 36.4% in model rats. In contrast to normal control, the pretreatment with phenobarbital did not affect acetaminophen and its metabolite levels in plasma and urine

in model rats. After the establishment of anhepatic model the serum direct bilirubin rose dramatically. Urinary bilirubin test was positive in model rats, but not in normal control. No changes were observed in serum total bilirubin and ratio of direct/total bilirubin after the pretreatment with ranitidine or phenobarbital 50 mg kg (-1), i.p. for 5 days in model rats. The results indicate that the glucuronide- and sulfate-acetaminophen formed in the extrahepatic tissues of model rats is 28.2% of normal control, serum free bilirubin can be transformed into conjugated bilirubin in extrahepatic tissues, and the regulation mechanism of phase II conjugating enzymes is different between the hepatic and extrahepatic tissues.

L8 ANSWER 20 OF 34 EMBASE
AN 2003453317 EMBASE
TI Regulatory Mechanisms Controlling Gene Expression Mediated by the Antioxidant Response Element.
AU Nguyen, Truyen (correspondence); Sherratt, Philip J.; Pickett, Cecil B.
CS Schering-Plough Research Institute, Kenilworth, NJ 07033, United States.
truyen.nguyen@spcorp.com; cecil.pickett@spcorp.com; philip.sherratt@spcorp.com
SO Annual Review of Pharmacology and Toxicology, (2003) Vol. 43, pp. 233-260.
Refs: 105
ISSN: 0362-1642 CODEN: ARPTDI
CY United States
DT Journal; General Review; (Review)
FS 022 Human Genetics
029 Clinical and Experimental Biochemistry
052 Toxicology
LA English
SL English
ED Entered STN: 11 Dec 2003
Last Updated on STN: 11 Dec 2003
AB The expression of genes encoding antioxidative and Phase II detoxification enzymes is induced in cells exposed to electrophilic compounds and phenolic antioxidants. Induction of these enzymes is regulated at the transcriptional level and is mediated by a

specific enhancer, the antioxidant response element or ARE, found in the promoter of the enzyme's gene. The transcription factor Nrf2 has been implicated as the central protein that interacts with the ARE to activate gene transcription constitutively or in response to an oxidative stress signal. This review focuses on the molecular mechanisms whereby the trancriptional activation mediated by the interaction between the ARE and NF-E2-related factor 2 (Nrf2) is regulated. Recent studies suggest that the sequence context of the ARE, the nature of the chemical inducers, and the cell type are important for determining the activity of the enhancer in a particular gene.

L8 ANSWER 21 OF 34 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
AN 2003051582 EMBASE
TI Drug metabolism and individualized medicine.
AU Srivastava, Pratima (correspondence)
CS Division of Pharmacokinetics, Drug Metab. Central Drug Res. Inst., Lucknow 1, India. pratima.srivastava@roswellpark.org
AU Srivastava, Pratima (correspondence)
CS Department of Pharmacology, Therapeutics Roswell Park Can. Inst., Buffalo, NY 14263, United States. pratima.srivastava@roswellpark.org
SO Current Drug Metabolism, (Feb 2003) Vol. 4, No. 1, pp. 33-44. Refs: 83
ISSN: 1389-2002 CODEN: CDMUBU
CY Netherlands
DT Journal; General Review; (Review)
FS 022 Human Genetics
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
006 Internal Medicine
LA English
SL English
ED Entered STN: 7 Feb 2003
Last Updated on STN: 7 Feb 2003
AB Drug metabolism refers to the biochemical transformation of a compound into another more polar chemical form. Absorption, distribution, metabolism and excretion comprise an integral part in understanding the

safety and efficacy of a potential new drug. Detailed in-depth knowledge of the Pharmacokinetics and Drug Metabolism of a new drug entity is considered a prerequisite to know the appropriate route of administration, correct dose etc. Sometimes there is (are) different/unwanted effect(s) of certain drugs in different populations. This is particularly true for the drug having narrow therapeutic index. Often these different effects are detrimental to an individual, thus termed as adverse drug reactions. After the raw draft of human genome has evolved, it has become increasingly clear that change(s) in the drug response between individuals, is due to the occurrence of genetic polymorphisms in the Phase I and II drug metabolizing enzymes, due to which distinct subgroups in the population differ in their ability to perform certain drug biotransformation reactions. The study about the occurrence of genetic polymorphisms in drug metabolizing enzymes is termed as Pharmacogenetics/ Pharmacogenomics. Pharmacogenetic characterization of particular drug can be both phenotypically or genotypically conducted in population groups. The study is very important to check the post-marketed drug withdrawal, if a particular percentage of population suffers from adverse drug reactions, and thus a lot of revenue be saved. The study also helps to find out Right Medicine for Right Individual or Individualized Medicine.

L8 ANSWER 22 OF 34 EMBASE
AN 2003006468 EMBASE
TI Application of DNA microarrays in pharmacogenomics and toxicogenomics.
AU Chin, Khew-Voon (correspondence)
CS Department of Medicine, Robert Wood Johnson Medical School, Univ. Med. and Dent. of New Jersey, New Brunswick, NJ 08901, United States. chinkv@umdnj.edu
AU Kong, A.-N. Tony
CS Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers,

State Univ. of New Jersey, Piscataway, NJ 08854, United States. Kongt@rci.
rutgers.edu
SO Pharmaceutical Research, (1 Dec 2002) Vol. 19, No. 12, pp. 1773-1778.
Refs: 30
ISSN: 0724-8741 CODEN: PHREEB
CY United States
DT Journal; General Review; (Review)
FS 022 Human Genetics
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 16 Jan 2003
Last Updated on STN: 16 Jan 2003
AB Many drugs or xenobiotics can induce specific or nonspecific cellular signal transduction events that activate various physiologic and pharmacologic responses including homeostasis, proliferation, differentiation, apoptosis, and necrosis. To minimize the insults caused by these xenobiotics, tissues and organs are equipped with protective mechanisms that either pump drugs out of the cells (e.g., the multidrug-resistant, mdr, family of proteins) or increase the level of detoxifying enzymes such as phase I and II drug-metabolizing enzymes (DMEs), after exposure to xenobiotics. This review discusses the molecular analysis of pharmaco- or toxicogenomic gene expression profiles following exposure to cancer chemotherapeutic and chemopreventive agents. We present the development of DNA microarray technology and its use in expression profiling of possible signal transduction events elicited by these compounds, and its potential future applications in drug discovery and development in the pharmaceutical industry.

L8 ANSWER 23 OF 34 EMBASE
AN 2001435183 EMBASE
TI Induction of xenobiotic enzymes by the map kinase pathway and the antioxidant or electrophile response element (ARE/EpRE).
AU Kong, A.-N. Tony (correspondence); Owuor, Edward; Yu, Rong; Hebbar, Vidya; Chen, Chi; Hu, Rong; Mandlekar, Sandhya
CS Center for Pharmaceutical Biotechnology, Department of Pharmaceutics and

Pharmacodynamics, University of Illinois at Chicago, Chicago, IL, United States. kongt@cop.rutgers.edu
AU Kong, A.-N. Tony (correspondence)
CS Department of Pharmaceutics, College of Pharmacy, Rutgers University, 160 Frelinghuysen Road, Piscataway, NJ 08854, United States. kongt@cop.rutgers.edu
AU Mandlekar, Sandhya
CS Department of Drug Metabolism and Pharmacokinetics, DuPont Pharmaceutical Company, Newark, DE, United States.
AU Kong, A.-N. Tony (correspondence)
CS Department of Pharmaceuticals, Rutgers University, Environ./Occup. Health Science Inst., 160 Frelinghuysen Road, Piscataway, NJ 08854, United States. kongt@cop.rutgers.edu
SO Drug Metabolism Reviews, (2001) Vol. 33, No. 3-4, pp. 255-271.
Refs: 71
ISSN: 0360-2532 CODEN: DMTRAR
CY United States
DT Journal; General Review; (Review)
FS 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 3 Jan 2002
Last Updated on STN: 3 Jan 2002
AB Cellular responses to xenobiotic-induced stress can signal proliferation, differentiation, homeostasis, apoptosis, or necrosis. To better understand the underlying molecular mechanisms after exposure to xenobiotics or drugs, we studied the signal transduction pathways, the mitogen-activated protein kinase (MAPK), and the basic leucine zipper transcription factor Nrf2, activated by different agents in the induction of Phase II drug metabolizing enzymes (DMEs). The MAPKs, characterized as proline-directed serine/threonine kinases, are essential components of signaling pathways that convert various extracellular signals into intracellular responses through serial phosphorylation cascades. Once activated, MAPKs can phosphorylate many transcription factors, such as c-Jun, ATF-2, and ultimately lead to changes in gene expression. Two classes of Phase II

gene inducers, which are also cancer chemopreventive agents, were studied:
(1) the phenolic antioxidants, namely butylated hydroxyanisole (BHA) and
its active de-methylated metabolite t-butylhydroquinone (tBHQ), and
phenolic flavonoids such as green tea polyphenols (GTP) and
(-)-epigallocatechin-3-gallate (EGCG); and (2) the naturally occurring
isothiocyanates, namely phenethyl isothiocyanate (PEITC), and
sulforaphane. BHA and tBHQ are both well-known phenolic antioxidants used
as food preservatives, and strongly activate c-Jun N-terminal kinase 1
(JNK1), extracellular signal-regulated protein kinase 2 (ERK2), or p38, in
a time- and dose-dependent fashion. Free radical scavengers
N-acetyl-L-cysteine (NAC), or glutathione (GSH), inhibited ERK2 activation
and, to a much lesser extent, JNK1 activation by BHA/tBHQ, implicating the
role of oxidative stress. Under conditions where MAPKs were activated,
BHA or GTP also activated ARE/EpRE (antioxidant/electrophile response
element), with the induction of Phase II genes such as
NQO. Transfection studies with various cDNAs encoding wild-type
or dominant-negative mutants of MAPKs and/or transcription factor Nrf2,
substantially modulated ARE-mediated luciferase reporter activity in the
presence or absence of phenolic compounds. Other phytochemicals including
PEITC, and sulforaphane, also differentially regulated the activities of
MAPKs, Nrf2, and ARE-mediated luciferase reporter gene activity and
Phase II enzyme induction. A model is proposed where
these xenobiotics (BHA, tBHQ, GTP, EGCG, PEITC, sulforaphane) activate the
MAPK pathway via an electrophilic-mediated stress response, leading to the
transcription activation of Nrf2/Maf heterodimers on ARE/EpRE enhancers,
with the subsequent induction of cellular defense/detoxifying genes
including Phase II DMEs, which may protect the cells
against toxic environmental insults and thereby enhance cell survival.
The studies of these signaling pathways may yield insights into the fate
of cells upon exposure to xenobiotics.

L8 ANSWER 24 OF 34 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights
reserved on STN
AN 2001398217 EMBASE
TI Induction by xenobiotics of phase I and phase
II enzyme activities in the human keratinocyte cell line NCTC
2544.
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SO Toxicology in Vitro, (2001) Vol. 15, No. 6, pp. 701-711.
Refs: 44
ISSN: 0887-2333 CODEN: TIVIEQ
PUI S 0887-2333(01)00084-4
CY United Kingdom
DT Journal; Article
FS 013 Dermatology and Venereology
029 Clinical and Experimental Biochemistry
052 Toxicology
LA English
SL English
ED Entered STN: 26 Nov 2001
Last Updated on STN: 26 Nov 2001
AB This study analyses the expression and induction of several
drug-metabolising enzyme activities involved in either phase
I or phase II biotransformations in NCTC 2544
human keratinocytes. The phase I activities
7-ethoxycoumarin O-deethylase (ECOD), 7-ethoxyresorufin
O-deethylase
(EROD) and 7-pentoxyresorufin O-depenthylase (PROD) were easily
detectable
in basal conditions. During incubations lasting up to 144 h in
the
presence of the classical cytochrome P450 inducers
β-naphthoflavone
(BNF), 3-methylcholanthrene (MC) and phenobarbital (PB), a
considerable
and significant increase in all the three activities was
observed. PROD
activity was induced up to 4.5-fold after 96 h in the presence
of PB. The
MC-induced ECOD and EROD activities were also dose-dependently
inhibited
by α-naphothflavone, which was given to the cells during the
incubation with CYP 1A1 inducers. Also the PB-induced PROD
activity was
decreased by the simultaneous addition of the CYP 2B inhibitor
metyrapone.

Both cytochrome P450 inhibitors were used at non-cytotoxic concentrations.
The phase II enzymes glutathione S-transferase,
aldehyde dehydrogenase and quinone reductase were all highly expressed and
inducible by MC. The exposure (24 h) of the cells to four hair dyes used
in cosmetic formulations resulted in a marked increase in ECOD activity.
All data give sustained evidence for the suitability of NCTC 2544 cell
line to skin toxicology studies.

L8 ANSWER 25 OF 34 EMBASE
AN 2001300138 EMBASE
TI Effect of onion consumption by rats on hepatic drug-metabolizing enzymes.
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SO Food and Chemical Toxicology, (2001) Vol. 39, No. 10, pp. 981-987.
Refs: 47
ISSN: 0278-6915 CODEN: FCTOD7
PUI S 0278-6915(01)00056-4
CY United Kingdom
DT Journal; Article
FS 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 13 Sep 2001
Last Updated on STN: 13 Sep 2001
AB Fruits and vegetables or their natural constituents which increase

detoxication enzymes and/or reduce activating enzymes are considered as good candidates to prevent chemically-induced carcinogenesis. In this study, rats were fed a diet supplemented with 20% onion powder for 9 days. Several cytochrome P450 (CYP)s enzymes (CYP 1A, 2B, 2E1, 3A), which are involved in carcinogen activation, were determined by measuring their enzyme activities using specific substrates. In addition, phase II enzymes activities such as UDP-glucuronosyltransferase (UGT) and glutathione S-transferase (GST), involved in detoxication of carcinogens, were measured. Protein levels of CYPs and GST A1/A2, A3/A5, M1, M2 and P1 were measured using antibodies in Western blots. Consumption of onion induced CYP 1A and CYP 2B activities while it decreased CYP 2E1 activity. This later modification was accompanied by a decrease of CYP 2E1 levels. The same dietary treatment caused a slight increase of the total GST activity. The relative proportions of GST subunits were modified. GST A1/A2 subunits were increased while GST A3/A5 and GST M2 subunits were decreased and GST M1 and P1 were not modified. Onion consumption also increased p-nitrophenol UGT activity. Taken together, these results suggest that the decrease of CYP 2E1 and the increase of phase II enzymes by onion can afford protection against some carcinogens, while the decrease of some GST subunits could increase the genotoxic effects of other chemicals. The modulating effect of onion could be ascribed to alk(en)yl polysulphides and/or glycosides of flavonols, which were identified in the onion powder.

L8 ANSWER 26 OF 34 EMBASE

AN 2001020162 EMBASE

TI Effect of organosulfur compounds from garlic and cruciferous vegetables on drug metabolism enzymes.

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SO Drug Metabolism and Drug Interactions, (2000) Vol. 17, No. 1-4, pp. 23-49.
Refs: 123
ISSN: 0792-5077 CODEN: DMDIEQ
CY Israel
DT Journal; General Review; (Review)
FS 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 1 Feb 2001
Last Updated on STN: 1 Feb 2001
AB The frequent consumption of cruciferous vegetables and garlic is associated with several health benefits. These foods contain organosulfur compounds that are known to affect the biotransformation of xenobiotics, and therefore can influence the toxicity and carcinogenicity of environmental chemicals. In this article, we review the effects of isothiocyanates and diallyl sulfide on xenobiotic metabolism and the enzymes involved in the process. Isothiocyanates and diallyl sulfide can modulate the levels of phase I and phase II drug-metabolizing enzymes by affectingthe transcriptional rates of their genes, the turnover rates of specific mRNAs or enzymes, or the enzyme activity. These compounds are not general enzyme inhibitors or inducers. They elicit selectivity in their mode of action. Elucidating the mechanisms involved in the alteration of drug-metabolizing enzymes by isothiocyanates and diallyl sulfide will increase our understanding of their possible effects on the biotransformation of drugs as well as the potential beneficial or detrimental effects of these organosulfur compounds.

L8 ANSWER 27 OF 34 EMBASE
AN 2000332593 EMBASE
TI Effects of oxazepam and acetaminophen on cicletanine metabolism in rat hepatocytes and liver microsomes.

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SO Fundamental and Clinical Pharmacology, (1999) Vol. 13, No. 5, pp. 571-576.
Refs: 21
ISSN: 0767-3981 CODEN: FCPHEZ
CY France
DT Journal; Article
FS 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 13 Oct 2000
Last Updated on STN: 13 Oct 2000
AB Cicletanine, a racemic furopyridine derivative synthesized as racemate, is
used as an antihypertensive agent. Its two enantiomers are involved in
the pharmacological effects of the drug. Cicletanine is
metabolized by conjugation enzyme systems (phase
II) into sulfoconjugated or glucuroconjugated enantiomers. As
oxazepam and acetaminophen are widely prescribed, especially to elderly
patients, these two drugs may be co-administered with cicletanine. The
metabolic profile and the kinetics of biotransformation were studied by
using rat hepatocytes and liver microsomes. Cicletanine was extensively
metabolized by rat hepatocytes. More than 80% of the drug was
biotransformed after a 3 h incubation. The formation of glucuroconjugated
metabolites was characterized by the following kinetic parameters, i.e.
V(max) = 2.05 ± 0.21 nmol/min/mg protein and K(m) = 287 ± 6.7 μM

for (-)-cicletanine, and V(max) = 1.44 ± 0.12 nmol/min/mg protein and K(m) = 171 ± 4.1 μM for (+)-cicletanine. Oxazepam inhibited the glucuronidation of cicletanine in both rat hepatocytes and liver microsomes with a competitive-type inhibition, i.e. K(i) = 129 ± 7.5 and 152 ± 19.7 μM for (-)-cicletanine and (+)-cicletanine, respectively. The co-incubation of acetaminophen with cicletanine showed that only sulfoconjugation was inhibited in rat hepatocytes. Glucuronidation was not modified by acetaminophen. As natriuric activity is due to sulfoconjugated (+)-cicletanine, acetaminophen could potentially modulate in vivo the pharmacological effect of cicletanine. The data of the in vitro study reported here suggested an interaction between cicletanine and oxazepam or cicletanine and acetaminophen. However, the clinical impact of such a drug interaction needs further evaluation. (C) 1999 Editions scientifiques et medicales Elsevier SAS.

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AN 2000056032 EMBASE

TI p38 Mitogen-activated protein kinase negatively regulates the induction of phase II drug-metabolizing enzymes that detoxify carcinogens.

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SO Journal of Biological Chemistry, (28 Jan 2000) Vol. 275, No. 4, pp.
2322-2327.
Refs: 56
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 24 Feb 2000
Last Updated on STN: 24 Feb 2000
AB Phase II drug-metabolizing enzymes, such as glutathione S-transferase and quinone reductase, play an important role in the detoxification of chemical carcinogens. The induction of these detoxifying enzymes by a variety of agents occurs at the transcriptional level and is regulated by a cis- acting element, called the antioxidant response element (ARE) or electrophile-response element. In this study, we identified a signaling kinase pathway that negatively regulates ARE-mediated gene expression. Treatment of human hepatoma HepG2 and murine hepatoma Hepa1c1c7 cells with tert-butylhydroquinone (tBHQ) stimulated the activity of p38, a member of mitogen-activated protein kinase family. Inhibition of p38 activation by its inhibitor, SB203580, enhanced the induction of quinone reductase activity and the activation of ARE reporter gene by tBHQ. In contrast, SB202474, a negative analog of SB203580, had little effect. Consistent with this result, interfering with the p38 kinase pathway by overexpression of a dominant-negative mutant of p38 or MKK3, an immediate upstream regulator of p38, potentiated the activation of the ARE reporter gene by tBHQ, whereas the wild types of p38 and MKK3 diminished such activation. In addition, inhibition of p38

activity augmented the induction of ARE reporter gene activity by tert-
butylhydroxyanisole, sulforaphane, and β-naphthoflavone. Thus, p38
kinase pathway functions as a negative regulator in the ARE-mediated
induction of phase II detoxifying enzymes.

L8 ANSWER 29 OF 34 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights
reserved on STN
AN 1999214990 EMBASE
TI Pharmacodynamics and toxicodynamics of drug action: Signaling in cell
survival and cell death.
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SO Pharmaceutical Research, (1999) Vol. 16, No. 6, pp. 790-798.
Refs: 122
ISSN: 0724-8741 CODEN: PHREEB
CY United States
DT Journal; General Review; (Review)
FS 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 8 Jul 1999
Last Updated on STN: 8 Jul 1999
AB In therapeutic response to drugs, the plasma concentration range leads to
the establishment of a safe and effective dosage regimen. Our hypothesis
is that by studying drug concentration-dependent effect on signal
transduction mechanisms, a better understanding of the beneficial
pharmacodynamic and adverse toxicodynamic responses elicited by the drug
may be achieved. Using two classes of chemopreventive compounds (phenolic
antioxidants and isothiocyanates), we illustrate the potential utility of
two signal transduction pathways elicited by these agents to
predict the pharmacodynamic effect (induction of Phase
II drug metabolizing enzymes) and the potential toxicodynamic
response (stimulation of caspase activity and cytotoxic cell death). At

lower concentration, phenolic antioxidants and isothiocyanates activate mitogen-activated protein kinase (MAPK; extracellular signal-regulated protein kinase 2, ERK2; and c-Jun N-terminal kinase I, JNK1) in a concentration- and time-dependent manner. The activation of MAPK by these compounds may lead to the induction of cell survival/protection genes such as c-jun, c-fos, or Phase II drug metabolizing enzymes. However, at higher concentrations, these agents activate another signaling molecule, ICE/Ced3 cysteine protease enzymes (caspases) leading to apoptotic cell death. The activation of these pathways may dictate the fate of the cells/tissues upon exposure to drugs or chemicals. At lower concentrations, these compounds activate MAPK leading to the induction of Phase II genes, which may protect the cells/tissues against toxic insults and therefore may enhance cell survival. On the other hand, at higher concentrations, these agents may activate the caspases, which may lead to apoptotic cell death, and have toxicity. Understanding the activation of these and other signal transduction events elicited by various drugs and chemicals may yield insights into the regulation of gene expression of drug metabolizing enzymes and cytotoxicity. Thus, the study of signaling events in cell survival (hemeostasis) and cell death (cytotoxicity) may have practical application during pharmaceutical drug development.

L8 ANSWER 30 OF 34 EMBASE

AN 1999194969 EMBASE

TI Cancer chemopreventive activity of resveratrol.

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SO Drugs under Experimental and Clinical Research, (1999) Vol. 25, No. 2-3,
pp. 65-77.
Refs: 93
ISSN: 0378-6501 CODEN: DECRDP
CY Switzerland
DT Journal; Conference Article; (Conference paper)
FS 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 17 Jun 1999
Last Updated on STN: 17 Jun 1999
AB Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a naturally occurring
compound shown to inhibit carcinogen-induced preneoplastic lesion formation in mouse mammary organ culture and tumorigenesis in the two-stage mouse skin model. Cancer chemopreventive potential was also
suggested in various assays reflective of the three major stages of
carcinogenesis. Anti-initiation activity was indicated by its antioxidant
and antimutagenic effects, inhibition of the hydroperoxidase function of
cyclooxygenase (COX), and induction of phase II
drug-metabolizing enzymes. Antipromotion activity was indicated by
antiinflammatory effects, inhibition of production of arachidonic acid
metabolites catalyzed by either COX-1 or COX-2, and chemical carcinogen-induced neoplastic transformation of mouse embryo fibroblasts. Antiprogression activity was demonstrated by its ability to
induce human promyelocytic leukemia (HL-60) cell differentiation.
Moreover, pretreatment of mouse skin with resveratrol significantly
counteracted 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative

stress, as evidenced by numerous biochemical responses. Resveratrol reduced the generation of hydrogen peroxide, and normalized levels of myeloperoxidase and oxidized-glutathione reductase activities. It also restored glutathione levels and superoxide dismutase activity. As judged by the reverse transcriptase-polymerase chain reaction, resveratrol selectively inhibited TPA-induced expression of c-fos and transforming growth factor-β1 (TGF-β1), but did not affect other TPA-induced gene products including COX-1, COX-2, c-myc, c-jun, and tumor necrosis factor-α. These data indicate that resveratrol may interfere with reactive oxidant pathways and/or modulate the expression of c-fos and TGF-β1 to inhibit tumorigenesis in mouse skin. As reported herein, in addition to the activities described above, resveratrol inhibited the de novo formation of inducible nitric oxide synthase (iNOS) in mouse macrophages stimulated with lipopolysaccharide. This finding suggests an additional mechanism by which resveratrol may function as a cancer chemopreventive agent.

L8 ANSWER 31 OF 34 EMBASE
AN 1998149319 EMBASE
TI Preclinical development of camptothecin derivatives and clinical trials in pediatric oncology.
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AU Pondarre, C.; Boland, I.; Cappelli, C.; Santos, A.; Thomas, C.; Morizet, J.; Gouyette, A.
SO Biochimie, (Mar 1998) Vol. 80, No. 3, pp. 271-280.
Refs: 66
ISSN: 0300-9084 CODEN: BICMBE
CY France
DT Journal; General Review; (Review)
FS 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index

038 Adverse Reactions Titles
007 Pediatrics and Pediatric Surgery
LA English
SL English
ED Entered STN: 2 Jun 1998
Last Updated on STN: 2 Jun 1998
AB Although the prognosis of childhood cancers has dramatically improved over the last three decades, new active drugs are needed. Camptothecins represent a very attractive new class of anticancer drugs to develop in paediatric oncology. The preclinical and clinical development of two of these DNA-topoisomcrase I inhibitors, ie topotecan and irinotecan, is ongoing in paediatric malignancies. Here we review the currently available results of this evaluation. Topotecan proved to be active against several paediatric tumour xenografts. In paediatric phase I studies exploring several administration schedules, myelosuppression was dose-limiting. The preliminary results of topotecan evaluation in phase II study showed antitumour activity in neuroblastoma (response rate: 15% at relapse and 37% in newly diagnosed patients with disseminated disease) and in metastatic rhabdomyosarcoma (40% in untreated patients). Topotecan-containing drug combinations are currently investigated. Irinotecan displayed a broad spectrum of activity in paediatric solid tumour xenografts, including rhabdomyosarcoma, neuroblastoma, peripheral primitive neuroectodermal tumour, medulloblastoma, ependymoma, malignant glioma and juvenile colon cancer. For several of these histology types, tumour-free survivors have been observed among animals bearing an advanced-stage tumour at time of treatment. The clinical evaluation of irinotecan in children is ongoing. Iinotecan undergoes a complex in vivo biotransformation involving several enzyme systems, such as carboxylesterase, UDPGT and cytochrome P450, in children as well as in adults. Preclinical studies of both drugs have shown that their activity was schedule-dependent. The optimal schedule of

administration is an issue that needs to be addressed in children. In conclusion, the preliminary results of the paediatric evaluation of camptothecin derivatives show very encouraging results in childhood malignancies. The potential place of camptothecins in the treatment of paediatric malignant tumours is discussed.

L8 ANSWER 32 OF 34 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
AN 1997312222 EMBASE
TI Cytochrome P450-dependent enzyme activities in normal adult human keratinocytes and transformed human keratinocytes.
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SO In Vitro Toxicology: Journal of Molecular and Cellular Toxicology, (1997) Vol. 10, No. 2, pp. 207-216.
Refs: 41
ISSN: 0888-319X CODEN: IVTOE4
CY United States
DT Journal; Article
FS 013 Dermatology and Venereology
005 General Pathology and Pathological Anatomy
052 Toxicology
LA English
SL English
ED Entered STN: 30 Oct 1997
Last Updated on STN: 30 Oct 1997
AB Human keratinocytes, which are the most abundant epidermal cell type, are increasingly used to study the cytotoxicity of topically applied compounds and preparations. The cytotoxicity of some compounds may be due to their metabolism in the skin, notably by keratinocytes known to express xenobiotic metabolizing enzymes (phase I and II). The use of normal adult human keratinocytes (NHK) can be restricted by the small number of cells isolated and by the donor variability. Both disadvantages can be overcome by amplifying the cells or by using cell lines. For pharmacological and/or toxicologic studies, the metabolic capacities of the cell model used may first be determined comparatively to

NHK. NHK isolated from breast skin, human keratinocyte cell lines immortalized either spontaneously (NCTC 2544, HaCaT) or by SV-40 transfection (SVK14) were studied for the presence of certain cytochrome P-450-dependent phase I enzyme activities. 7-ethoxycoumarin O-deethylase (ECOD), 7-ethoxyresorufin O-deethylase (EROD), and pentoxyresorufin O-dealkylase (PROD) activities were measured after various culture conditions (subculture and cryopreservation). Induction by 3-methylcholanthrene (3-MC) as well as the effect of a mono-oxygenase activity inhibitor (proadifen), were also evaluated. Our results show that after subculture (up to the second passage), NHK retain CYP-dependent ECOD (1.2 to 3.6 pmol of product/h/mg protein) and EROD (1.6 to 5.3 pmol of product/h/mg protein) enzyme activities. These enzyme activities remain inducible by 3-MC (1 μM) in the same proportions as in primary culture (450 to 760 pmol of product/h/mg protein for ECOD and 220 to 365 pmol of product/h/mg protein for EROD). Similar studies of human keratinocyte cell lines also showed the presence of ECOD and EROD activities. These activities were inducible by 3-MC, but less so than in primary culture. PROD activity was not detected. These results are discussed with respect to the use of subcultured NHK or transformed keratinocyte cell lines, for toxicity screening studies of compounds that could be metabolized by the skin.

L8 ANSWER 33 OF 34 EMBASE
AN 1996142924 EMBASE
TI Culture and drug biotransformation capacity of adult human keratinocytes from post-mortem skin.
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CS BIOPREDIC, Rennes-Atalante-Villejean, 14-18 rue Jean Pecker, 35000 Rennes, France.
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AU Watier, E.
CS Serv. Chir. Plastique R., Hopital Sud, 35033 Rennes, France.

AU Patoux-Pibouin, M.
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SO British Journal of Dermatology, (1996) Vol. 134, No. 5, pp. 831-836.
Refs: 25
ISSN: 0007-0963 CODEN: BJDEAZ
CY United Kingdom
DT Journal; Article
FS 013 Dermatology and Venereology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 11 Jun 1996
Last Updated on STN: 11 Jun 1996
AB The aim of this study was to analyse viability, growth, differentiation
and drug metabolic capacity of cultured human keratinocytes obtained from
post-mortem skin. Epidermal cells were prepared from 1-day post-mortem
paired sun-exposed (outer) and sun-protected (inner) sites of the upper
arm, of donors aged 47-80 years. The percentage of viable cells obtained
from post-mortem skin was only slightly lower than that usually obtained
for keratinocytes isolated from fresh skin, and no alterations of
epidermal markers were noted. Keratinocytes isolated post-mortem from
non-exposed skin had a higher viability (78 versus 73%), and a more active
proliferation, while their attachment rate, keratin composition, lipid
synthesis capacity and transglutaminase activity levels were similar to
those of epidermal cells obtained from the sun-exposed skin.
Keratinocytes isolated from postmortem skin expressed various
phase I and II activities at levels similar to those
obtained with keratinocytes isolated from fresh skin while drug
metabolizing enzyme activities were consistently higher
in sun-exposed compared to sun-protected cells. The results support the
conclusion that skin collected post-mortem can represent an alternative
source of viable and functional epidermal cells, and that the functional
changes that occur in adult keratinocytes habitually exposed to the sun,
affect much more strongly the drug metabolism capacity than the expression

of differentiation markers.

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AN 1996135818 EMBASE
TI Effects of dietary broccoli on human in vivo drug metabolizing enzymes:
Evaluations of caffeine, oestrone and chlorzoxazone metabolism.
AU Kall, M.A. (correspondence); Vang, O.; Clausen, J.
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SO Carcinogenesis, (1996) Vol. 17, No. 4, pp. 793-799.
ISSN: 0143-3334 CODEN: CRNGDP
CY United Kingdom
DT Journal; Article
FS 016 Cancer
017 Public Health, Social Medicine and Epidemiology
029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 20 May 1996
Last Updated on STN: 20 May 1996
AB Ingestion of cruciferous vegetables may prevent chemically induced
carcinogenesis by their influence on specific cytochrome P450 enzymes
(CYP) and phase II drug metabolizing enzymes in humans
and rodents. Thus CYP enzymes are involved in transformation of
procarcinogens, mutagens, steroid hormones and a large variety of other
endogenous and exogenous components. In order to learn more about the
influence of cruciferous vegetables on drug metabolizing enzymes in man
two CYP enzymes previously suggested to be induced by vegetables were
selected in an in vivo experiment in humans. Sixteen healthy non-smoking
subjects, two females and 14 males, were exposed to three different types
of diets and afterwards assayed for CYP1A2 catalysed caffeine metabolites
and for CYP2E1 catalysed 6-hydroxylation of chlorzoxazone. Further,
2-hydroxyoestrone:16α-hydroxyoestrone ratios were determined in
urine by means of a monoclonal antibody-based enzyme immunoassay. The
three dietary periods were: (A) a customary home diet; (B) a 6 day
standard diet avoiding well-known dietary inducers and inhibitors of CYP;

(C) a 12 day dietary supplement to the standard diet of 500 g/day broccoli. The average 6-hydroxychlorzoxazone:chlorzoxatone ratio decreased by 21% ($P < 0.05$) after diet B compared with diet A in a 2 h plasma sample after ingestion of 500 mg chlorzoxazone. The ratio increased by 19% after diet C, however, this was not statistically significant. The caffeine metabolic ratio (CMR) was determined in urine 6 h after ingestion of 100 mg caffeine. The mean CMR increased by 5.5% when changing from diet A to diet B. When shifting to diet C the mean CMR increased a further 19% ($P < 0.0005$). The average 2-hydroxyoestrone:16α-hydroxyoestrone ratio decreased by 1.3% when comparing diet A with diet B. Daily broccoli intake increased the ratio by 29.5% ($P < 0.05$). A low correlation of CMR with the 2-hydroxyoestrone:16α-hydroxyoestrone ratio indicates that human CYP1A2 and other CYP enzymes involved in oestrone 2-hydroxylation are induced by dietary broccoli. On the other hand, the catalytic activity of CYP2E1 is not affected to the same degree by dietary broccoli.

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.91	166.18

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-8.20

STN INTERNATIONAL LOGOFF AT 16:29:31 ON 20 AUG 2009